Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note REG2006-14

Pinoxaden

The active ingredient pinoxaden and associated end-use product AXIAL 100EC Herbicide, containing 100 g/L pinoxaden, as well as ADIGOR Adjuvant for the control of grass weeds in durum wheat, spring wheat and barley have been granted temporary registration under the Pest Control Products Regulations.

This Regulatory Note provides a summary of data reviewed and the rationale for the proposed regulatory decision regarding these products.

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6605C
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.pmra-arla.gc.ca
Information Service:
1-800-267-6315 or 613-736-3799
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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has carried out an assessment of available information in accordance with the Pest Control Products Regulations and has found it sufficient to allow a determination of the safety, merit and value of pinoxaden, the associated end-use product AXIAL 100EC Herbicide, containing 100 g/L pinoxaden, and ADIGOR Adjuvant (A12127S formulation). This active ingredient and the associated end-use product were reviewed as part of a Joint Review with the United States Environmental Protection Agency (USEPA). The PMRA has concluded that the use of pinoxaden, AXIAL 100EC Herbicide and ADIGOR Adjuvant (A12127S formulation) in accordance with the label has merit and value consistent with the Pest Control Products Regulations and do not entail an unacceptable risk of harm. Therefore, based on the considerations outlined above, the use of pinoxaden, AXIAL 100EC Herbicide and ADIGOR Adjuvant (A12127S formulation) for the control of grass weeds in durum wheat, spring wheat and barley is proposed for temporary registration pursuant to the Pest Control Products Regulations.

Methods for analyzing pinoxaden in environmental media are available to research and monitoring agencies upon request to the PMRA.

Syngenta Crop Protection Canada Inc. will be carrying out additional chemistry, water solubility, environmental chemistry and value studies as a condition of this temporary registration. Following the review of this information, the PMRA will publish a proposed registration decision document (PRDD) and request comments from interested parties before proceeding with a final regulatory decision.

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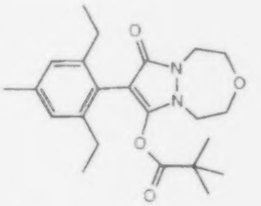
1.0 The Active Substance, its Properties and Uses

1.1 Identity of the Active Substance and Impurities

Active substance	Pinoxaden
Function	Herbicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	2,2-dimethyl-propionic acid 8-(2,6-diethyl-4methyl-phenyl)-9-oxo-1,2,4,5-tetrahydro-9H-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-yl ester
2. Chemical Abstracts Service (CAS)	8-(2,6-diethyl-4-methylphenyl)-1,2,4,5-tetrahydro-7-oxo-7*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepin-9-yl 2,2-dimethylpropanoate
CAS number	243973-20-8
Molecular formula	$C_{23}H_{32}N_2O_4$
Molecular weight	400.5
Structural formula	
Nominal purity of active	98.0%
Identity of relevant impurities of toxicological, environmental or other significance	Impurities of human health or environmental concern as identified in Section 2.13.4 of DIR98-04 and TSMP Track 1 substances as identified in Appendix II of DIR99-03 are not expected to be present in this product.

1.2 Physical and Chemical Properties of Active Substances and End-use Product(s)

1.2.1 Physical and Chemical Properties of the Active Substance

Property	Result
Colour and physical state	Light beige
Odour	Sweet odour

Property	Result
Melting point or range	120.5–121.6°C
Density	1.16×10^3 kg/m^3 at 24°C
Vapour pressure	2.0×10^{-7} Pa at 20°C 4.6×10^{-7} Pa at 25°C
Henry's law constant at 20°C	9.21×10^{-7} Pa m^3/mole ($1/H = 1.1 \times 10^6$)
Ultraviolet (UV)– visible spectrum	**Conditions** λ_{max} Neutral solution 210, 258 Acidic solution 210, 254 Basic solution 220, 252 No absorption maximum between 350 and 750 was observed in any of the three solutions.
Solubility in water at 25°C	200 mg/L
Solubility in organic solvents at 25°C	**Solvent** **Solubility (g/L)** Acetone 250 Dichloromethane > 500 Ethyl acetate 130 Hexane 1.0 Methanol 260 Octanol 140 Toluene 130
n-Octanol–water partition coefficient (K_{ow}) at 25°C	$\log K_{ow} = 3.2$
Dissociation constant (pK_a)	None, no dissociable moiety.
Stability (temperature, metal)	The product is chemically stable in the presence of iron, aluminium and their ions for at least 14 days. Stable when stored for 14 days at 54°C.

1.2.2 Physical and Chemical Properties of the End-use Products

Property	AXIAL 100EC Herbicide	ADIGOR Adjuvant (A12127S Formulation)
Colour	Yellow orange	Not provided
Odour	Thymol like odour	Aromatic odour

Property	AXIAL 100EC Herbicide	ADIGOR Adjuvant (A12127S Formulation)
Physical state	Liquid	Liquid
Formulation type	Emulsifiable concentrate	Emulsifiable concentrate
Nominal guarantee	Pinoxaden: 100 g/L	Rape see oil methyl ester: 48.8% Ethoxylated alcohols, C16-18 and C18 unsaturated: 28.2%
Formulants	The product does not contain any USEPA or PMRA List 1 formulants or formulants known to be TSMP Track 1 substances. It contains 55.65% Naphthalene Depleted Aromatic Solvent, a USEPA and PMRA List 2 formulant.	The product does not contain any USEPA or PMRA List 1 formulants or formulants known to be TSMP Track 1 substances. It contains 23% depleted aromatic solvent, a USEPA and PMRA List 2 formulant.
Container material and description	1 L, 5 L, 10 L, 15 L, 15 L, 55 L, 115 L, 200 L and bulk fluorinated high-density polyethylene (HDPE) containers	5.7 L, 11.4 L, 200 L and bulk fluorinated high-density polyethylen (HDPE) containers
Density or specific gravity	1.03 g/cm^3 at 20°C	0.922 g/cm^3 at 20°C
pH of 1% dispersion in water	5.3 (1% dispersion in water at 25°C)	Expected to be neutral
Oxidizing or reducing action	These products do not contain any oxidizing or reducing agents.	
Storage stability	Data showed that the product is stable when stored for 2 weeks at 54°C in a hermetically closed glass bottle and for one year at 20°C in fluorinated HDPE packaging.	Expected to be stable
Explodability	No explosive materials present in the products	

1.3 Details of Uses

Pinoxaden is a Weed Science Society of America (WSSA) Group 1 herbicide belonging to a new class of Acetyl CoA carboxlylase (ACCase) inhibitors, the 'phenylpyrazolins' (PPZ). This new chemistry was developed in the mid 1990s, after the development of aryloxyphenoxypropianates (APP) in 1975 and cyclohexodione (CHD) in 1986.

Pinoxaden is the active component in the end-use product (EP) AXIAL 100EC Herbicide, an emulsifiable concentrate (EC) formulation that is based on a concentration of 100 grams pinoxaden per litre of formulated product. The use of an adjuvant (Merge or the in-house adjuvant ADIGOR 'Booster' [A12127S formulation]) is required to maximize herbicide uptake and to enable the active ingredient to reach the target site in sufficient concentrations.

AXIAL 100EC Herbicide is to be applied as a postemergence treatment for the control of specific grass weeds in spring wheat (*Triticum aestivum*), durum wheat (*Triticum turgidum*) and barley (*Hordeum vulgare*) in the Prairie provinces and the Peace River, Okanagan and Creston Flats regions of British Columbia. AXIAL 100EC Herbicide must be applied with the new adjuvant ADIGOR Adjuvant (A12127S formulation; Registration Number 28151) or Merge (Registration Number 24702) at a rate of 700 mL/ha in a water volume of 50 to 100 litres per hectare, with a maximum of one application per year using ground equipment only. It is to be applied to actively growing weeds, when spring wheat, durum wheat and barley, as well as labelled weed species, are between the 1- and 6-leaf stage, prior to the 4th tiller.

There are two rates of application for AXIAL 100EC Herbicide. AXIAL 100EC Herbicide applied at a rate of 40 g a.i./ha will control Persian darnel (*Lolium persicum*). Applied at a rate of 60 g a.i./ha, AXIAL 100EC Herbicide will control wild oats (*Avena fatua*), green foxtail (*Setaria viridis*), yellow foxtail (*Setaria glauca*), volunteer oats (*Avena sativa*), volunteer canary seed (*Phalaris canariensis*) and proso millet (*Panicum miliaceum* L.).

The data provided indicated that a rate lower than 60 g a.i./ha of AXIAL 100EC Herbicide may provide acceptable control of wild oats, green foxtail, yellow foxtail, volunteer oats, volunteer canary seed and proso millet. Additional data are requested to establish the lowest effective rate to control these weeds.

There are no crop rotation limitations for the year following application of AXIAL 100EC Herbicide.

AXIAL 100EC Herbicide may be tank-mixed with one of the following broadleaf herbicides:
- Refine Extra at 15 g a.i./ha
- Refine Extra + MCPA ester at 15 + 350 g a.i./ha
- Express Pack at 7.5 + 396 g a.i./ha
- Frontline Herbicide Tank Mix at 5 + 420 g a.i./ha
- Buctril M at 560 g a.i./ha
- Thumper at 560 g a.i./ha
- Mextrol 400M at 560 g a.i./ha

- Okay 450M (renamed Mextrol 450) at 562 g a.i./ha
- MCPA ester at 420–550 g a.i./ha
- MCPA amine at 420–550 g a.i./ha
- 2,4-D ester at 560 g a.i./ha
- Estaprop at 1019 g a.i./ha
- Prestige Herbicide Tank Mix at 144 + 660 g a.i./ha
- Curtail M at 660 g a.i./ha
- Trophy at 108 + 560 g a.i./ha

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Substance as Manufactured

Three high performance liquid chromatography (HPLC) methods with ultra violet (UV) detection and two GC methods with flame ionization detection (FID) were provided for the analysis of the active ingredient and process related impurities. With the exception of one impurity for which the quantitation was based on the response factor of the active ingredient, the quantitation of the active ingredient and all other impurities was by the external standard method.

The method for the active was accurate as demonstrated by overall mean recovery range of 99.7–100.5%, precise as shown by the relative standard deviation (RSD) of 0.23%, linear in the range of 50–150% of the active concentration in the product and specific as demonstrated by the absence of any interference peaks around the response peak of the active.

Two HPLC methods for four impurities were assessed to be accurate as shown by the recovery data, which ranged from 87.5 to 132.1% and precise as evidenced by the mean RSD of 1.25%. These two methods also had a wide linear range, from 1.91 to 33 µg/mL. In addition, the methods were specific as demonstrated by the absence of any interference peaks around the response peaks of the analytes of interest in the chromatograms provided and sensitive with a limit of detection (LOD) <0.1% for all four analytes.

Two gas chromatography (GC) methods for one impurity and residual solvent were shown to be linear in range 1.99–483.9 µg/mL, accurate with the recovery data ranging from 90.6 to 113.7%, precise with average RSD 2.15% and specific as demonstrated by the absence of any interference peaks around the response peak of this impurity. The methods sensitivity was < 0.1% for all analytes.

2.2 Method for Formulation Analysis

An HPLC method with UV detection was provided for the determination of the active ingredient in the formulation. Quantitation of the active ingredient was by external standard. The method had a wide linearity range of 50–150% of the active concentration in the product, good precision with RSD of 0.31% and accuracy as shown by a mean recovery of 100.1%. The specificity was shown by the absence of analytical interferences in the representative chromatograms.

The method was assessed to be fully validated and acceptable for use as enforcement analytical method.

The enforcement analytical method for the determination of the adjuvant actives in the adjuvant product has not been provided. Based on the provided rationale and on the fact that the quality and consistency of the adjuvant will be maintained by requiring that each supplier furnish a certificate of analysis to ensure that the formulant meets established raw material specifications, the requirement for submission of the enforcement analytical method has been waived.

2.3 Methods for Residue Analysis

2.3.1 Methods for Environmental Residue Analysis

A liquid chromatography with tandem mass spectrometry system (LC/MS/MS) analytical method was developed for the determination of the active ingredient pinoxaden (NOA 407855) and its degradates 8-(2,6-diethyl-4-methylphenyl)tetrahydro-8-hydroxypyrazolo[1,2-d][1,4,5]oxadiazepine-7,9-dione (NOA 447204) and 8-(2,6-diethyl-4-methyl-phenyl)-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepine-7,9-dione (NOA 407854) along with [(5-chloro-8-quinolinyl)oxy]acetic acid 1-methylhexyl ester (CGA 185072 safener) and its degradate [(5-chloro-8-quinolinyl)oxy]acetic acid (CGA 153433) in soil.

Soil samples from Grant County, Washington, and Grand Forks County, North Dakota, were used to evaluate the method. The samples were extracted with a 50/50% (v/v) acetone/water and cleaned with NH_2 solid-phase extraction (SPE) column followed by Nexus SPE column. A 60/40% (v/v) acetone/water citrate buffer was used to extract CGA 153433 from the samples. A portion of the extract was partitioned with methylene chloride and after evaporation cleaned with a C18 SPE cartridge. Recovery data for all remaining analytes demonstrated good accuracy, overall mean recovery ranged from 73.2 to 90.7% and precision, overall RDS percentages ranged from 5.5 to 11.3%, at 0.5, 5 and 50 ppb fortification levels. No quantifiable interferences were observed in the chromatograms of blank and soil control. The method has a limit of detection of 5 pg and a limit of quantification of 0.5 ppb for all analytes. Based on the validation data and chromatograms the method was assessed to be specific, precise, accurate and sensitive. It is acceptable for use as postregistration monitoring method.

2.3.2 Multiresidue Methods for Residue Analysis

The behaviour of pinoxaden and the metabolites M2 (NOA 407854), M4 (SYN 505164), M6 (SYN 502836) and M10 (SYN 505887) was evaluated through the multiresidue methods (MRMs) of the United States Food and Drug Administration's *Pesticide Analytical Manual*, Volume I. Pinoxaden, M2, M4, M6 and M10 were not evaluated through protocols A and G because they do not possess an N-methylcarbamate structure (Protocol A) or a urea moiety (Protocol G). Also, pinoxaden and the metabolites M2, M4 and M10 were not screened through Protocol B as they do not possess a carboxylic acid or phenolic moiety. As M6 is a carboxylic acid, it was tested through Protocol B (Section 402). Both M6 and methylated M6 displayed no acceptable GLC (gas liquid chromatography) response on the following systems:

- DG5—GLC equipped with a DB-1 column (100% methyl siloxane) and a nitrogen phosphorus detector (NPD);
- DG13—capillary GLC equipped with a DB-17 column (50% phenyl, 50% methyl siloxane) and an electron capture detector (ECD); or
- DG18—capillary GLC equipped with a DB-225 column (50% cyanopropyl phenyl, 50% methyl siloxane) column and an ECD.

The results from Protocol C indicated that pinoxaden chromatographed with an acceptable relative retention time to chlorpyrifos on DG5 and DG13 at Level II temperature (230°C). Metabolite M2 chromatographed with an acceptable relative retention time to chlorpyrifos on DG5 system at Level II temperature. Metabolite M4 chromatographed with an acceptable relative retention time to chlorpyrifos on DG5 system at Level II temperature and on DG13 system (elevated temperature was not required with the DG13 system). M10 resulted in multiple peaks when tested on DG5 and DG13 systems and displayed no response (no peak) when tested on DG18. No further testing in protocols D and E was performed for M6 and M10.

Pinoxaden, M2 and M4 were tested through Protocol D. Significant interferences were observed at or near the retention times of the three compounds in wheat forage controls. Pinoxaden, M2 and M4 were not recovered through Protocol D. No further testing in Protocol E was performed for M2 and M4.

Pinoxaden was tested through Protocol E. Pinoxaden was not recovered from any of the C1 or C2 eluants.

Multiresidue methods are not suitable for the analysis of pinoxaden and the metabolites M2, M4, M6 and M10.

2.3.3 Methods for Residue Analysis of Plants and Plant Products

Based on the wheat metabolism studies, the residue of concern (ROC) for enforcement and risk assessment purposes was defined as pinoxaden and metabolites M2, M4 (free and conjugate) and M6 in cereal matrices.

Three analytical methodologies (REM 199.02, REM 199.03 and 117-01) were proposed for the analysis of residues of pinoxaden (as metabolite M2) and metabolites M2, M4, M6 and M10 (Methods REM 199.02 and 199.03 only) in cereal matrices. All three methods possessed the same extraction procedure consisting of acid hydrolysis (1N HCl) by boiling under reflux for two hours, which is consistent with the methodology used during the wheat metabolism studies. Under these conditions, pinoxaden, the parent molecule, was converted to the metabolite M2. Thus, the methods analyzed for pinoxaden as M2 (common moiety).

Briefly, Method REM 199.02 involved extracting homogenized crop samples with 1N HCl under reflux for two hours. Following filtration (if necessary), the pH of the extract was raised by addition of 3% ammonia solution, and the solution was left to settle for half an hour. The analysis of the resulting extract was performed by reversed-phase HPLC using a column-switching system connected via a pneumatically and thermally assisted electrospray ionization (ESI) to a tandem mass spectrometer (HPLC-MS/MS). It should be noted that two analytical sequences with different chromatographic conditions were necessary to quantify the four analytes. The limit of quantitation (LOQ) of the method was reported as 0.02 ppm in cereal whole plants, ears, stalks and straw and as 0.01 ppm in cereal grains for each analyte. No LOD was established. This method was found to give recoveries within the acceptable range of 70–120% for the analysis of M2, M4, M6 and M10 in all the wheat matrices (whole plant, straw and grain) when spiked at the LOQ and at 10× the LOQ. The standard deviations (ranging from 2 to 10%) measured with respect to recoveries at each spiking level were indicative of the method having satisfactory repeatability. Good linearity was observed in the range of 0.35 to 20 ng/mL for each of the analytes ($r^2 > 0.999$). No independent laboratory validation (ILV) of this method was submitted. Based on the submitted recovery data, analytical method REM 199.02 used for the quantitation of residues of M2, M4, M6 and M10 is considered acceptable as a data-gathering method in cereal matrices.

Briefly, Method REM 199.03 involved extracting homogenized crop samples with 1N HCl under reflux for two hours. The pH of the extract was raised by addition of 3% ammonia solution. The extract was centrifuged, filtered using a Vectaspin filtration tube and cleaned up onto an Oasis HBL SPE cartridge eluted with dichloromethane, ethyl acetate and formic acid (80:20:0.5, v/v/v). The eluates were evaporated in the presence of 1M HCl solution and diluted with water prior to final analysis by HPLC-MS/MS. The LOQ of the method was reported as 0.02 ppm in cereal whole plants, ears, stalks and straw, and as 0.01 ppm in cereal grains and cereal process fractions for each analyte. The LOD was estimated at 0.002 ppm for all analytes in the matrices tested. Individual recoveries for M2, M4, M6 and M10 were all within the acceptable range of 70–120% for the analysis of barley whole plant samples at spiking levels of 0.02 ppm (LOQ; n = 5 for each analyte at each spiking level) and 2.00 ppm. Barley grain samples were spiked at levels of 0.01 ppm (LOQ) and of 0.50 ppm. Individual recoveries in barley grain were all within 70–120%. Recoveries for barley straw spiked at the LOQ (0.02 ppm) were generally within 70–120% except for the analysis of M2 where 3 values were below 70%. At the 0.50 ppm spiking level, M6 and M10 each had 1 value <70%. However, the standard deviations (ranging from 2% to 11%) measured with respect to recoveries at each spiking level were indicative of the method having satisfactory repeatability. Good linearity was observed in the range of 0.00125 to 0.5 µg/mL for each of the analytes ($r^2 > 0.999$). No ILV of this method was submitted. Based on the submitted recovery data, analytical method REM 199.03 used for the quantitation of residues of M2, M4, M6 and M10 is considered acceptable as a data-gathering method in cereal matrices.

Briefly, Method REM 117-01 involved extracting homogenized crop samples with 1N HCl (or 1N HCl and acetonitrile [90:10, v/v]) under reflux for 2 hours. For determination of combined residues of pinoxaden and M2 (as M2), an aliquot of the extract was filtered (if the solution was not clear) and, after dilution with water, the final fraction was injected onto a reversed-phase C_{18} to ODS-3 two-column switching HPLC-MS/MS system for analysis. The C_{18} column was eluted with formic acid aqueous solution (0.1%) and methanol (75:25, v/v), and the ODS-3 column with formic acid aqueous solution (0.05%) and methanol (50:50, v/v). For determination of M4 and M6, an aliquot of the extract was filtered (if the solution was not clear) and the extract was cleaned up with a preconditioned SCX (2) SPE cartridge (elution with acetonitrile and water

[25:75, v/v]). The purified extract was then evaporated to an aqueous solution and the concentrated sample was loaded onto a preconditioned C_8 SPE cartridge (elution with acetonitrile and 0.2% formic acid [50:50, v/v]). The eluate was evaporated to an aqueous solution and after dilution with 0.2% formic acid, the final fraction was injected onto a SCX to C_8 two-column switching HPLC-MS/MS system for analysis. The SCX column was eluted with water and acetonitrile (85:15, v/v), and the C_8 column with formic acid aqueous solution (0.05%), methanol and acetonitrile (67:18:15, v/v/v). The LOQ of the method was reported as 0.02 ppm in cereal forage, hay and straw and as 0.01 ppm in cereal grains for each analyte. The LOD of the method was reported as 0.005 ng for M4 and M6, and 0.00125 ng for M2.

Method 117-01 was found to give recoveries within the acceptable range of 70–120% for the analysis of M2, M4 and M6 in all the cereal matrices (grain, forage, hay and straw) when spiked at the LOQ and up to 100× the LOQ. The standard deviations (ranging from 3% to 13%) measured with respect to recoveries at each spiking level were indicative of the method having satisfactory repeatability. Good linearity was observed in the range of 0.00005 to 0.00300 ng/μL for each of the analytes (r^2 >0.998). The independent laboratory successfully validated Method 117-01 at the first or second attempt using wheat (forage, straw, grain and aspirated grain fractions) and barley (hay and grain) matrices. Furthermore, based on the extraction efficiency data provided, both analytical methods REM 199.02 (or REM 199.03) and 117-01 were successfully radio-validated using wheat matrices (grain, husk and straw collected from the metabolism studies) as they were capable of extracting bioincurred residues of the four metabolites of interest (M2, M4, M6 and M10). Based on the submitted recovery data, on the ILV results and on the radio-validation results, analytical method 117-01 used for the quantitation of residues of M2, M4 and M6 is considered acceptable as the enforcement method in cereal matrices.

2.3.4 Methods for Residue Analysis of Food of Animal Origin

In ruminant matrices, the ROC for enforcement and risk assessment purposes was defined as pinoxaden and the metabolites M2 and M4 (free and conjugates). In poultry matrices, the ROC for enforcement and risk assessment purposes was defined as pinoxaden and metabolites M2, M4 (free and conjugates) and M6.

Method T001530-03 is proposed as both the data-gathering method and the enforcement method in livestock matrices for the determination of the two major pinoxaden metabolites, M4 and M6.

Briefly, matrix samples are refluxed with 1N HCl for two hours to extract the residues. An aliquot of the filtered extract is passed through a preconditioned SCX (2) SPE column for clean-up. The eluate as well as the acetonitrile and water (25:75, v/v) rinse are combined and evaporated to an aqueous solution by rotary evaporation. The aqueous solution is loaded onto a preconditioned C_8 SPE column and the column is eluted with acetonitrile and 0.2% formic acid (50:50, v/v). The eluate is evaporated to an aqueous solution by rotary evaporation. The final volume is adjusted with 0.2% formic acid and aliquots are measured directly by injection into an HPLC-MS/MS system using the Multiple Reaction Monitoring function (retention time of

M4 ~13.8 minutes, with m/z of 333 → 303 and retention time of M6 ~15.5 minutes with m/z 345 → 173).

The method is sensitive to the proposed analytes, with low LOQs (0.01 ppm in milk and 0.02 ppm in tissues and eggs) and LODs (0.005 ng) for both analytes. Recoveries from milk samples spiked at the LOQ ranged from 87% to 100% for M4 (n=6) and from 98% to 108% for M6 (n=6). Coefficients of variation in milk spiked at LOQ were 12% and 5% for M4 and M6, respectively. In tissues and eggs spiked at the LOQ, recoveries ranged from 81% to 104% for M4 and 80% to 105% for M6, with coefficients of variation ranging from 2% to 8% (n=6 for each matrix and analyte). Recoveries in all matrices spiked at levels up to 10× the LOQ ranged from 69% to 110%, with coefficients of variation ranging from 3% to 9% for both analytes.

Control chromatograms were supplied for all matrices, and no interferences were noted at or near the retention times of the analytes, indicating that the method is specific for the metabolites in question. In addition, the analysis of reagent blanks demonstrated no interference originating from the chemicals or analytical instruments. The detector response was demonstrated to be linear in the range of 0.005–0.5 ng, with coefficients of determination (r^2) greater than 0.9997 for both analytes.

The ILV of Method T001530-03 successfully demonstrated the reliability of the method for the analysis of residues of M4 and M6 in beef muscle, beef fat, milk and eggs on the first attempt. The registrant submitted a scientifically acceptable rationale to waive the requirement of a radio-validation study for this method. Method T001530-03 is considered acceptable as a data-gathering method for the determination of M4 and M6 in livestock matrices. However, Method T001530-03 is considered unacceptable as the enforcement method because it does not analyze for all the components of the ROC in livestock matrices: pinoxaden, M2, M4 and M6. For Method T001530-03 to be considered as the enforcement method in livestock matrices, the registrant must provide the following:

- a method that would analyze for pinoxaden as well as metabolites M2 and M4 in ruminant matrices;
- a method that would analyze for pinoxaden as well as metabolites M2, M4 and M6 in poultry matrices; and
- recovery data validating the implemented changes to the method in livestock matrices.

3.0 Impact on Human and Animal Health

3.1 Integrated Toxicological Summary

A detailed review of the toxicological database for pinoxaden was conducted. The database was complete, consisting of a full array of toxicity studies currently required for regulatory purposes. The studies were carried out in accordance with currently acceptable international testing protocols and good laboratory practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to the chemical.

Pinoxaden was of low toxicity by the oral, dermal and inhalation routes of exposure. It was non-irritating to the skin, was severely irritating to eyes and was not a dermal sensitizer.

The metabolites, M6 and M10, were of low acute oral toxicity, while M3 was of slight acute oral toxicity. The impurity, SYN 519312, was of low acute oral toxicity.

The formulated product, AXIAL 100EC Herbicide, was of low acute toxicity by the oral, dermal and inhalation routes. It was moderately irritating to the eyes and skin, and was not a dermal sensitizer.

The adjuvant, ADIGOR Adjuvant (A12127S formulation), was of low acute toxicity by the oral, dermal and inhalation routes. It was mildly irritating to the skin and minimally irritating to the eyes. ADIGOR Adjuvant (A12127S formulation) was determined to be a skin sensitizer.

Absorption and excretion of single or repeat oral doses of pinoxaden in the rat was very rapid. More than 90% of the oral gavage dose was absorbed from the gastrointestinal tract. Approximately 90% of the absorbed dose was excreted in urine and feces in 72 hours, and excretion was nearly complete in 7 days. Excretion in the urine ranged from 59% to 78% and in feces ranged from 20% to 25%. Tissue distribution data indicated no significant accumulation in the body. The biliary excretion study did not indicate enterohepatic circulation. No parent compound was found in the excreta. The major metabolite in the urine and feces was the hydrolysis product M2. The major metabolites in urine were M2 (65–85%) and M4 (5–13%) and in the feces M2 (50–70%) and M4 (25–35%) depending on the dose. There were no sex related differences in the absorption, distribution, excretion or qualitative profile of the metabolites. Studies conducted in the mouse and rabbit indicated that the metabolic profile is similar in these species to that of the rat.

A short-term dermal study showed no skin irritation in any of the test groups after repeated applications of pinoxaden to the shaved skin of rats.

A waiver was granted for the short-term inhalation study based on the low volatility, particle size and low acute toxicity of pinoxaden.

In subchronic and chronic studies, pinoxaden elicited effects on the liver and kidney in rodents. Liver effects included: increased absolute and relative liver weight, increased glycogen deposition, decreased cholesterol, increased serum bilirubin and increased aspartate aminotransferase and plasma alkaline phosphatase activity. Kidney effects included ketonuria, tubular nephropathy, increased absolute and relative kidney weight, renal tubular casts, polymorphonuclear infiltration, single cell necrosis, cysts, cortical tubular basophilia/dilation/atrophy, ectasia pelvis, transitional cell hyperplasia and decreased plasma glucose. Generalized toxicity was observed in rats and mice as decreased body weight/body-weight gain, increased water consumption, decreased food efficiency/consumption and increased piloerection. Rats also exhibited increased leucocytosis, increased hematocrit and increased adrenal and testes weights. Mice also had an increase in eosinophils. The dogs exhibited body-weight loss, decreased food consumption, salivation at dosing, pale and thin appearance, increased incidence of regurgitation and vomiting as well as were cold to touch.

Subchronic studies on the metabolite M3 in the rat elicited effects in the liver and kidney. Liver effects included the following:

- increased absolute and relative weight;
- increased incidence in minimal to slight non-zonal eosinophilia/reduced glycogen;
- increased gamma-glutamyl transferase;
- decreased triglycerides;
- increased cholesterol;
- enlarged livers; and
- panlobular reduced glycogen/increased eosinophilia.

Kidney effects included decreased glucose, increased proteinuria, increased incidence and severity of ketonuria, increased absolute and relative kidney weight and minimal chronic progressive nephropathy. General effects observed were decreased food consumption, decreased water consumption, decreased leucocytes, neutrophils and basophils and decreased body-weight gain and food efficiency.

Subchronic studies conducted on the metabolite M6 showed no treatment-related effects.

The long-term study in the rat provided no evidence of treatment-induced oncogenicty. The mouse dietary and gavage carcinogenicity studies were considered inadequate for evaluating the carcinogenic potential of pinoxaden because the dietary mouse study did not reach the maximum tolerated dose and the gavage study had significant gavage errors making interpretation of the results difficult. However, there was no evidence of carcinogenicty in the rat study, the mouse gavage study was conducted up to 750 mg/kg bw/day without a significant increase in tumours being observed, the dietary study was tested up to 166 mg/kg bw/day without signs of systemic toxicity with the exception of a slight decrease in body weight and body-weight gain and, in the 90-day mouse feeding study tested at the limit dose, no severe toxicity was observed. The PMRA would not expect a new study to reveal any positive data with regard to carcinogenicty in light of the weight-of-evidence. Therefore, at this time, the PMRA does not require any further studies to be conducted.

Pinoxaden and metabolite M3 did not cause point mutations, were not associated with unscheduled DNA synthesis in vitro and were negative in a mouse mammalian chromosome micronucleus test. Both elicited a positive response in the in vitro chromosomal aberration assay. In the same battery of genotoxicity studies, metabolite M10 was positive for forward mutation but negative in a battery of four other tests, and metabolite M6 was negative for all conducted tests. The impurity, SYN 519312, did not induce micronuclei in a mouse micronucleus assay. As no mode of action could be determined and all positive results were seen only in the in vitro studies, the overall weight-of-evidence is that pinoxaden is not genotoxic.

In the rat developmental toxicity studies, maternal findings included decreased body-weight gains (uncorrected and corrected for gravid uterus weight), increased piloerection and food consumption. In addition, one female was euthanized for humane reasons. Fetal observations consisted of delays in skeletal ossification in the skull and hind digits and decreased body weight. There was no indication that neonates were quantitatively more sensitive than adults to pinoxaden. Reproductive function and litter parameters were not influenced by treatment. In the rabbit developmental toxicity studies, increased mortality, decreased body weight, decreased body-weight gain (uncorrected and corrected for gravid uterus weight), increased early resorptions, increased postimplantation loss and decreased food consumption were observed in the dams and the fetal body weights were decreased. There was no indication that neonates were quantitatively more sensitive than adults to pinoxaden; however, the early resorptions were indicative of a single dose effect. There was no evidence of any treatment-related irreversible structural changes in either species; therefore, pinoxaden was not considered to be teratogenic in rats or rabbits.

There was no evidence of increased sensitivity in the offspring in the two-generation reproductive toxicity study. Renal effects were observed in the parental generation that included increased water consumption, increased absolute and relative kidney weight, increased incidence of slight to marked dilation of the renal pelvis, increased incidence of renal tubular atrophy and increased incidence of chronic nephropathy. Offspring effects included decreased body weight and body-weight gain.

In acute and subchronic neurotoxicity studies, treatment with pinoxaden did not result in any neuropathy or clinical signs of neurotoxicity. No adverse effects were observed in any of the studies.

3.2 Determination of Acceptable Daily Intake

The recommended acceptable daily intake for pinoxaden is 0.1 mg/kg bw/day. The developmental rabbit study was considered the most appropriate study to assess chronic dietary exposure. The no observed adverse effect level (NOAEL) was 30 mg/kg bw/day based on moribundity (one rabbit), increased abortions, decreased body weights/body-weight gains and food consumption in the dams and increased incidence of complete early litter resorptions at the lowest observed adverse effect level (LOAEL) of 100 mg/kg bw/day. The standard uncertainty factor of 100 is applied to account for intraspecies and interspecies variability, and an additional 3-fold safety factor is recommended to account for the severity of effect (resorptions) seen in this study. This provides a margin of safety of 300× to the NOAEL for this endpoint.

The acceptable daily intake proposed is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{UF}} = \frac{30\ \text{mg/kg bw/day}}{300} = 0.1\ \text{mg/kg bw/day}$$

3.3 Acute Reference Dose

The recommended acute reference dose for pinoxaden is 0.1 mg/kg bw/day for females 13+. The developmental rabbit study was considered the most appropriate study to assess chronic dietary exposure. The NOAEL was 30 mg/kg bw/day based on moribundity (one rabbit), increased abortions, decreased body weights/body-weight gains and food consumption in the dams and increased incidence of complete early litter resorptions at the LOAEL of 100 mg/kg bw/day. The standard uncertainty factor of 100 is applied to account for intraspecies and interspecies variability, and an additional 3-fold safety factor is recommended to account for the severity of effect (resorptions) seen in this study. This provides a margin of safety of 300× to the NOAEL for this endpoint.

The acute reference dose proposed is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{UF}} = \frac{30\text{ mg/kg bw/day}}{300} = 0.1\text{ mg/kg bw/day}$$

3.4 Toxicological Endpoint Selection: Occupational and Bystander Risk Assessment

Short- and Intermediate-term Occupational Dermal and Inhalation Exposures

For short- and intermediate-term occupational exposure via the dermal and inhalation routes, the rabbit developmental study with a NOAEL of 30 mg/kg bw/day was considered most appropriate. Parental effects observed included moribundity (one rabbit), increased abortions, decreased body weights/body-weight gains and food consumption in the dams and increased incidence of complete early litter resorptions at the LOAEL of 100 mg/kg bw/day. The standard uncertainty factor of 100 is applied to account for intraspecies and interspecies variability, and an additional 3-fold safety factor is recommended for the protection of females 13+ based on the resorptions seen in this study. This provides a safety of 300× to the NOAEL for this endpoint. Therefore, the target margin of exposure (MOE) for these scenarios is 300.

Dermal Absorption

The applicant submitted three dermal absorption studies: one rat in vivo study, one rat in vitro study and a human in vitro study. Based on the rat in vivo study, a 40% dermal absorption value was selected for use in the exposure assessment based on radioactivity found in the urine, feces, cage wash, bandages, gastrointestinal tract, carcass, skin and tape strips from the high dose (400 $\mu g/cm^2$), 10-hour exposure and 34-hour sacrifice group. An amount of 5.3% of the radioactivity was found in the skin.

3.5 Impact on Human and Animal Health Arising from Exposure to the Active Substance or to its Impurities

3.5.1 Operator Exposure Assessment

AXIAL 100EC Herbicide contains pinoxaden at a guaranteed concentration of 100 g a.i./L. It is a liquid formulation for the control of certain grassy weeds on spring wheat, durum wheat and barley by ground application. AXIAL 100EC Herbicide must be applied with the registered Merge® Adjuvant or the proposed ADIGOR Adjuvant (A12127S formulation) at a rate of 700 mL/ha. Typical equipment used for ground application of herbicides to wheat and barley is a groundboom sprayer pulled behind an open or closed cab tractor. The product is packaged in 1 L, 5 L, 10 L, 15 L, 55 L, 115 L, 200 L, and bulk fluorinated high-density polyethylene (HDPE) containers. The product will be applied once per year early in the season at a maximum rate of 600 mL/ha (0.060 kg a.i./ha). Farmers have potential for short-term exposure to pinoxaden while mixing, loading and applying. Custom applicators have potential for intermediate term exposure.

Exposure to AXIAL 100EC Herbicide during mixing, loading and applying by groundboom equipment was estimated using the Pesticide Handlers Exposure Database (PHED) Version 1.1. The PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates. To estimate exposure for the groundboom use scenario, appropriate subsets were created from the mixer/loader and applicator database files of the PHED. The PHED was subset to represent two exposure scenarios:

- mixer/loader—liquid open mixing/loading; and
- applicator—open cab groundboom.

All data were normalized for kilogram of active ingredient handled. Unit exposures are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part. The primary route of exposure was dermal, with inhalation accounting for a maximum of 3.0% of total deposition.

The exposure estimates and MOEs for farmers and custom applicators mixing/loading and applying AXIAL 100EC Herbicide using groundboom equipment are summarized in Table 3.5.1.1.1.

Table 3.5.1.1.1 Scenario-Specific Exposure Estimates and MOEs for Farmers and Custom Applicators Mixing, Loading and Applying AXIAL 100EC Herbicide to Wheat and Barley

Exposure Scenario	PHED Total Unit Exposure[1] (µg a.i./kg a.i. handled)	Exposure Pattern (kg a.i. handled/day)	Daily Exposure[2] (mg a.i./kg bw/day)	MOE[3]
Farmer mixer/loader/applicator: Open pour, liquid, open cab, groundboom				
Mixer/loader—single layer, gloves Applicator—single layer, no gloves	36.21	150 ha/day at 0.060 kg a.i. /ha = 9 kg a.i. /day	4.7×10^{-3}	6500

Exposure Scenario	PHED Total Unit Exposure[1] (µg a.i./kg a.i. handled)	Exposure Pattern (kg a.i. handled/day)	Daily Exposure[2] (mg a.i./kg bw/day)	MOE[3]
Custom applicator mixer/loader/applicator: Open pour, liquid, open cab, groundboom				
Mixer/loader—single layer, gloves Applicator—single layer, no gloves	36.21	300 ha/day at 0.060 kg a.i. /ha = 18 kg a.i. /day	9.3×10^{-3}	3200

[1] Sum of mixer + loader + applicator dermal and inhalation exposures incorporating a dermal absorption factor of 40%.

[2] Calculated as [PHED total × exposure pattern] / body weight (70 kg).

[3] MOE = NOAEL of 30 mg/kg bw/day / daily exposure, target MOE = 300.

The MOEs for farmers and custom applicators using AXIAL 100EC Herbicide on wheat and barley for short-term and intermediate-term durations are acceptable (MOEs > 300). This is based on the mixer/loader wearing a single layer of clothing (long-sleeved shirt and long pants) with gloves, and the applicator wearing a single layer of clothing without gloves using open cab equipment. The use of the new ADIGOR Adjuvant (A12127S formulation) was found to be of acceptable risk to the user provided additional personal protective equipment is worn to mitigate irritation and sensitization hazards.

To a limited extent, pinoxaden may react with water in the spray tank and empty containers to form pivalic acid. Pivalic acid is an eye and respiratory tract irritant. Based on the small amount of pivalic acid that can be formed and the slow rate of this reaction, the PMRA concluded that pivalic acid was of negligible risk to the user.

3.5.2 Bystanders

There are no proposed residential uses. Therefore, a residential exposure assessment was not required.

3.5.3 Workers

Bystander exposure and risk during and after application of this product were considered minimal compared to mixer/loader/applicator and re-entry worker and, therefore, not quantified.

3.5.4 Consumers

There are no proposed residential uses. Therefore, an aggregate risk assessment was not required.

4.0 Residues

4.1 Nature of the Residue in Plants

Wheat

Four wheat metabolism studies were performed using either spring wheat or winter wheat with pinoxaden radiolabelled either in the pyrazol, phenyl or oxadiazepine rings and treated at different timings of application (fall, early spring and late spring) and at various growth stages (BBCH 13, BBCH 21, BBCH 37–39 and BBCH 49). Furthermore, wheat crop parts were sampled over a wide range of preharvest intervals (PHIs), from immature forage and ears to mature grain, husk and straw.

The first study was comprised of a field study and two non-guideline substudies (cell culture experiment and stem injection experiment). In the field study, pinoxaden radiolabelled in the pyrazol ring was applied as a fall application to winter wheat plants at growth stage BBCH 13 (three leaves unfolded) maintained outdoors, at a rate of 69 g a.i./ha. Total radioactive residues (TRRs) in wheat forage were 6.731 ppm (0-day PHI), 0.304 ppm (14-day PHI), 0.109 ppm (42-day PHI) and 0.011 ppm (209-day PHI). When harvested at maturity (264-day PHI), TRRs in wheat matrices were 0.004 ppm (grain), 0.029 ppm (husk) and 0.036 ppm (straw). Due to the low residues in grain, no characterization was attempted. Representative homogenized samples of each of the wheat matrices were extracted with acetonitrile/water (80:20, v/v), releasing >80% of the TRRs in forage, ~64% of the TRRs in straw and ~79% of the TRRs in husk samples. In the forage samples, immediately after treatment (0 days after treatment [DAT]), the predominant metabolite observed was M2 (4.47 ppm, ~66% TRRs), while the unmetabolized parent molecule accounted for only 36.2% of the TRRs (2.44 ppm), illustrating that pinoxaden was rapidly metabolized. By day 42, the parent compound had all undergone metabolism as no pinoxaden was detected in the forage samples. At this interval, M5 and M9 were the major metabolites observed representing 30.2% and 15.1% of the TRRs, respectively. At 209 DAT, the predominant metabolites in forage were M8 (0.0012 ppm, 10.8% TRRs) and M3 (0.002 ppm, 19.2% TRRs); no M5 was detected. In the mature straw samples (264 DAT), the predominant metabolites were M3 and M10, representing 11.1% and 14.2% of the TRRs, respectively. The postextraction solids (35.1% of TRRs, 0.013 ppm) were further extracted by incubation with 1N HCl for 6 hours at 100°C releasing an additional 12.9% of the TRRs. Analysis of the organosoluble fraction by thin-layer chromatography (TLC) identified M10 as the major portion of the fraction. The predominant metabolites in mature wheat husks (264 DAT) were M3 and M10 representing 31.4% and 12.6% of the TRRs, respectively. The postextraction solids (26.6% of TRRs, 0.0077 ppm) were not analyzed further.

The second study was comprised of two field studies and a non-guideline substudy (stem injection experiment). In the field studies, pinoxaden radiolabelled in the phenyl ring was applied as a spring application to winter wheat plants at growth stage BBCH 49 (first awns visible), maintained outdoors, at a rate of either 64 g a.i./ha or 318 g a.i./ha. At the lower rate of application, TRRs in wheat forage were 1.909 ppm (0-day PHI), 1.950 ppm (7-day PHI), 1.434 ppm (14-day PHI) and 2.396 ppm (28-day PHI). In ears, TRRs were 0.743 ppm (28-day PHI). In mature wheat (55 DAT), the TRRs in grain, husk and straw were 0.246 ppm, 3.133 ppm and

5.491 ppm, respectively. At the higher rate of application, TRRs in wheat forage were 8.914 ppm (14-day PHI) and 7.700 ppm (28-day PHI) and in ears were 2.837 ppm (28-day PHI). In mature wheat (55 DAT), the TRRs in grain, husk and straw were 0.845 ppm, 11.843 ppm and 15.896 ppm, respectively. Representative homogenized samples of each of the wheat matrices were extracted with acetonitrile/water (80:20, v/v), releasing >89% of the TRRs in forage, >60% of the TRRs in grain, >72% of the TRRs in straw and >67% of the TRRs in husk samples. The postextraction solids were subjected to harsh acid and base hydrolyses. Immediately after treatment (0 DAT forage), the predominant metabolites observed were M2 (~23% TRRs) and M4 (~64% TRRs), while the unmetabolized parent molecule accounted for only 9.8% of TRRs, illustrating that pinoxaden was rapidly metabolized. The predominant metabolites observed in all the samples were M4 and M5.

In the third study, pinoxaden radiolabelled either in the phenyl ring or the oxadiazepine ring was applied to spring wheat plants at growth stage BBCH 21 (initial tillering), maintained outdoors, at a rate of 60 g a.i./ha (phenyl) or 58 g a.i./ha (oxadiazepine). In the phenyl radiolabel study, TRRs in wheat forage were 4.420 ppm (0-day PHI), 0.834 ppm (14-day PHI) and 0.290 ppm (28-day PHI). In the oxadiazepine radiolabel study, TRRs in wheat forage amounted to 2.910 ppm (0-day PHI), 0.635 ppm (14-day PHI) and 0.155 ppm (28-day PHI). Representative homogenized forage samples were extracted with acetonitrile/water (80:20, v/v). Residues were extractable at ≥92% in all the forage samples. The parent compound could only be detected in the forage sample harvested at the 0-DAT interval. The metabolic profiles observed with the two different radiolabels were almost identical (except for minimal quantitative differences) as no label-specific metabolites were identified. Furthermore, the results were comparable to the results observed in the two previous wheat metabolism studies.

In the fourth study, pinoxaden radiolabelled either in the phenyl ring or the oxadiazepine ring was applied to spring wheat plants at growth stage BBCH 37–39 (flag leaf just visible to flag leaf fully unrolled), maintained outdoors, at a rate of 62 g a.i./ha (phenyl) or 66 g a.i./ha (oxadiazepine). In the phenyl radiolabel study, TRRs in wheat forage were 3.447 ppm (0-day PHI) and 1.021 ppm (14-day PHI). In mature wheat (67 DAT), the TRRs in grain, husk and straw were 0.142 ppm, 0.428 ppm and 0.908 ppm, respectively. In the oxadiazepine radiolabel study, TRRs in wheat forage amounted to 3.885 ppm (0-day PHI), 1.948 ppm (7-day PHI), 1.051 ppm (14-day PHI) and 1.211 ppm (28-day PHI). TRRs in ears amounted to 0.285 ppm (28-day PHI). In mature wheat (67 DAT), the TRRs in grain, husk and straw were 0.165 ppm, 0.381 ppm and 1.296 ppm, respectively. In the study conducted with the phenyl radiolabel, residues were extractable at ≥95% of the TRRs in the forage samples and at ≥78% of the TRRs in the mature wheat grain, husk and straw samples leaving 21.8%, 23.8% and 22.2% of the TRRs, respectively, as non-extractable residues. In the study conducted with the oxadiazepine radiolabel, residues were extractable at ≥93% of the TRRs in the forage samples and at ≥70% of the TRRs in the mature wheat grain, husk and straw samples leaving 18.7%, 27.0% and 27.8% of the TRRs, respectively, as non-extractable residues. The non-extractable residues in straw were further investigated with acid hydrolysis and fractionation of cellulose and lignin.

In wheat forage samples, immediately after treatment (0-DAT forage), the predominant metabolite observed was M2 (~72% TRRs for the phenyl radiolabel and ~79% TRRs for the oxadiazepine radiolabel). The parent compound was detected up to the 14-day interval. The other two predominant metabolites in forage were M4 and M5.

The predominant metabolite in straw was identified as M4 (both radiolabels). In husks, M4 and M6 were the major metabolites observed (both radiolabels). Further analysis of the straw non-extractable residues showed that a significant amount could be released by acid hydrolysis. The major part of the hydrolysate partitioned into dichloromethane, which revealed M4 and M6 as being the most abundant metabolites. Furthermore, 2.8% and 7.1% of the TRRs, released by base hydrolysis, was characterized as cellulose and lignin, respectively. The predominant fractions in mature wheat grain were the polar fraction I_1 (~26% TRRs for the phenyl label and ~35% TRRs for the oxadiazepine label), M5 and M6. To further characterize the polar fraction I_1 and the non-extractable residues in grain samples, whole grain samples were directly hydrolyzed with 1N HCl. Extractable residues from the phenyl label study consisted almost entirely of M4 and M6 and from the oxadiazepine label consisted of M4, M5 and M6 revealing that fraction I_1 contained no unknown or label-specific structures.

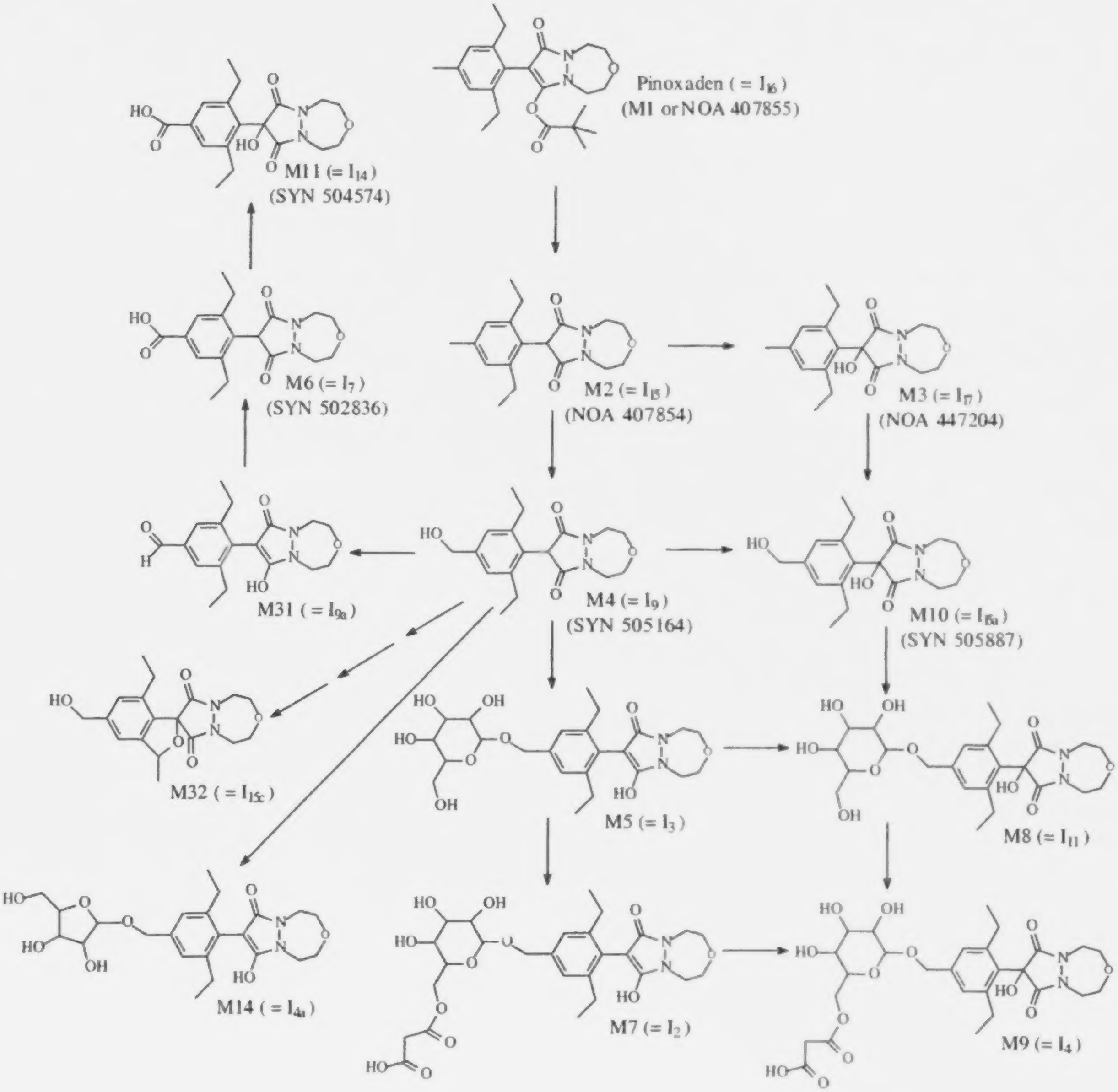
Briefly, pinoxaden was metabolized rapidly to M2 (ester hydrolysis). M2 was then hydroxylated, leading to M4, which was further conjugated to a sugar, yielding M5 (predominant metabolite observed in 14-DAT and 28-DAT forage samples; both radiolabels). An array of minor metabolites were also observed comprising M3, M6, M7, M8, M9, M10, M11 and several unknowns at very low levels.

Metabolic Profile Differences Between the Field Experiment and the Stem Injection Study

Pinoxaden was readily absorbed by the leaves of the plant as well as taken up (degradation products) by the roots to finally be translocated through the whole plant and into the grain. When the metabolic profiles in husks and straw from the field experiment and the stem injection study were compared, differences were noted. In the stem injection study, the predominant metabolites were identified as M4, M5 (glucose-conjugate of M4) and M6 (transformation product of M4), whereas in the field experiment the major compounds were M3 and M10 (methyl-hydroxy analog of M3). The metabolite M3 was also identified as the predominant metabolite in the soil sample taken at plant maturity. Accordingly, M3 could probably have been taken up from the soil by the plant, thus explaining its presence in the field experiment. Aside from this difference, the two substudies demonstrated similar metabolic pathways, differing primarily in the route of absorption rather than inherent metabolic activity.

Based on the findings of the wheat metabolism studies, the ROC for risk assessment and enforcement purposes was defined as pinoxaden (as M2), and the metabolites M2, M4 (free and conjugate) and M6 in cereal matrices. The metabolism of pinoxaden in cereal crops is well understood.

Figure 1 Proposed Metabolic Profile of Pinoxaden in Wheat (forage, grain, husks and straw)



4.2 Confined Accumulation in Rotational Crops

Three confined crop rotation trial studies were carried out with ^{14}C-pinoxaden radiolabelled either in the phenyl or the oxadiazepine ring. Depending on the study design, diverse rotational crops were used—mustard leaves, lettuce, radish, turnip, spring or winter wheat—and various plantback intervals (PBIs) were tested—15 days, 30 days, 120 days, 170 days and 365 days.

In the first study, pinoxaden (phenyl radiolabel) was applied to bare soil (clay loam) at a rate of 60 g a.i./ha. Lettuce and radish were planted 30 and 120 DAT, spring wheat was planted 30, 120 and 365 DAT, and winter wheat was planted 177 DAT. TRRs at the 30-DAT interval ranged from 0.001 ppm (radish root) to 0.035 ppm (spring wheat fodder), while at the 120-DAT interval, TRRs ranged from <0.001 ppm (radish root) to 0.038 ppm (spring wheat fodder). TRRs at the 177-DAT and 365-DAT intervals were all <0.005 ppm. Characterization of the TRRs revealed that the parent molecule, pinoxaden, was not detected in any of the samples and that no single metabolite fraction exceeded 0.01 ppm at any PBI. The following metabolites were identified: M2 (lettuce), M3 (lettuce, radish, spring wheat), M8 (spring wheat), M9 (spring wheat), M10 (spring wheat), M11 (spring wheat) and M32 (spring wheat).

In the second study, pinoxaden (oxadiazepine radiolabel) was applied to bare soil (clay loam) at a rate of 66 g a.i./ha. Lettuce and radish were planted 29 and 120 DAT, spring wheat was planted 29, 120 and 361 DAT, and winter wheat was planted 168 DAT. TRRs at the 29-DAT interval ranged from 0.002 ppm (radish root) to 0.077 ppm (spring wheat fodder), while at the 120-DAT interval, TRRs ranged from <0.001 ppm (radish root) to 0.032 ppm (spring wheat fodder). TRRs at the 168-DAT and 361-DAT intervals were all <0.005 ppm. Characterization of the TRRs revealed that the parent molecule, pinoxaden, was not detected in any of the samples and that no single metabolite fraction exceeded 0.01 ppm at any PBI, except in spring wheat forage at the 29-day PBI where M3 was found at levels of 0.024 ppm.

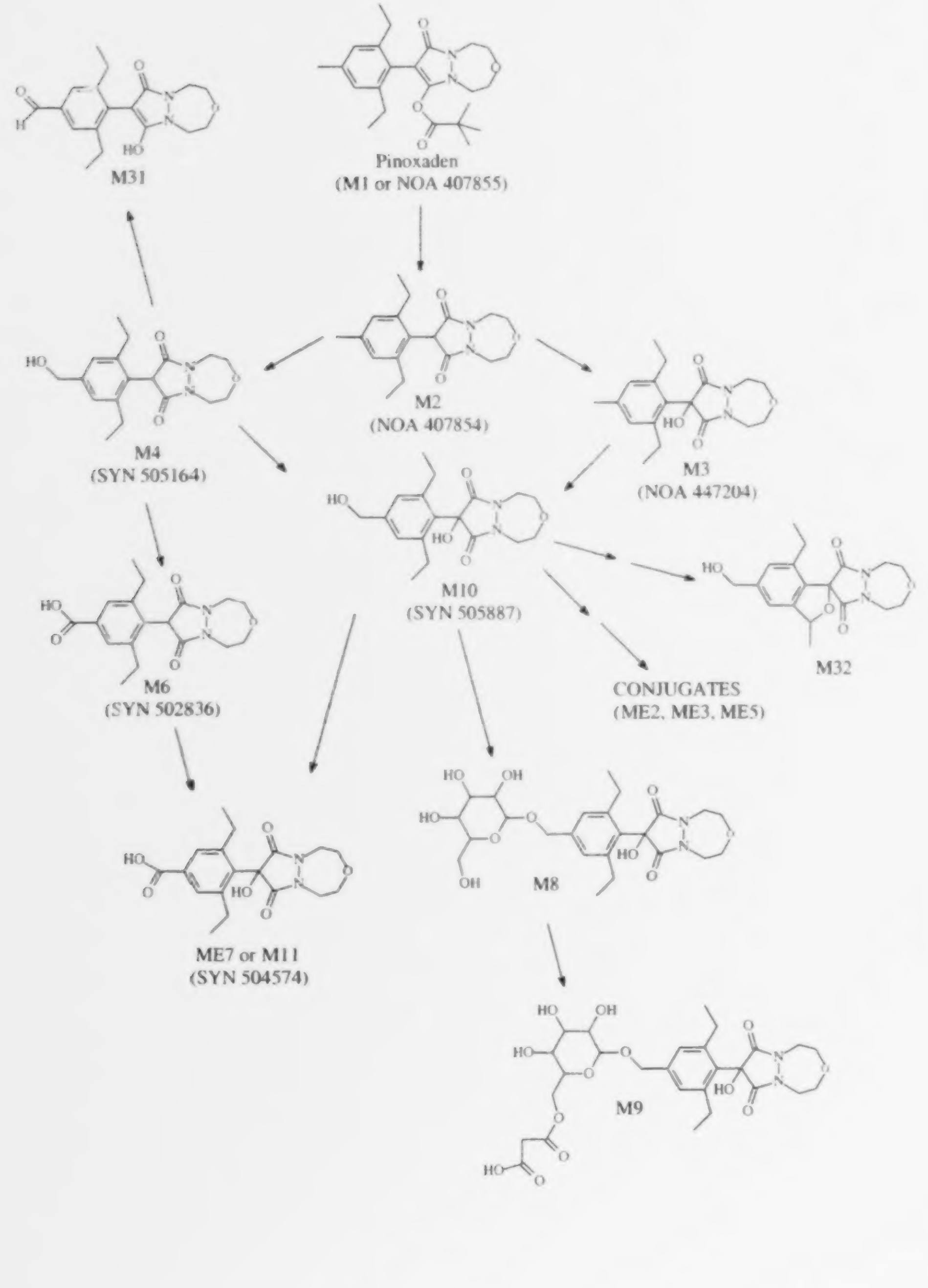
In the third study, pinoxaden (phenyl and oxadiazepine radiolabels) was applied to bare soil (silty clay loam) at a rate of 70 g a.i./ha. Three rotational crops were planted in soil that was aged for 15 days: mustard, turnip and spring wheat. TRRs ranged from 0.004 ppm (turnip root) to 0.069 ppm (spring heat fodder). Characterization of the TRRs revealed that the parent molecule, pinoxaden, was not detected in any of the samples. M3, M8, M10 and M11 were identified in most samples and were common to both radiolabels. Conjugates of M10 (ME2, ME3 and ME5) were also observed in the aqueous fraction and M6 was released from the fodder postextraction solids. The magnitude of the residues in the rotational crops from the confined crop rotation studies did not trigger a need for field accumulation studies.

The metabolic pathway of pinoxaden in secondary crops proceeded via similar processes as that in the primary crop, wheat. The metabolism of pinoxaden proceeded predominantly via hydrolysis of the ester moiety of the parent molecule giving M2, which was subsequently hydroxylated either at the 4-methyl group of the phenyl moiety yielding M4 or at the position 3 of the pyrazol moiety yielding M3. These two steps proceeded very fast in soil, resulting in M3 being the predominant metabolite observed in soil. It was suggested that M3 may have been taken up from the soil by the secondary crops, explaining why most of the metabolites identified were derivatives of M3. M3 and M4 were further hydroxylated to M10. M10 was conjugated with glucose, leading to M8. M9 resulted from the malonylation of M8. M10 was also conjugated leading to ME2, ME3 and ME5. Another metabolic pathway resulted from the oxidation of the methyl-hydroxy function of M10 to the corresponding carboxylic acid M11 (ME7) or from the oxidation of M4 to the carboxylic acid M6 and M11 (ME7). A minor metabolic pathway resulted from the oxidation of the ethyl side chain of M10 followed by cyclisation to M32.

Based on the findings of the confined accumulation in rotational crop studies, the ROC in rotational crops (secondary crops) for risk assessment and enforcement purposes was defined as pinoxaden (as M2), and the metabolites M2 and M3 (free and conjugate).

Based on these results, no PBI will be required on the AXIAL 100EC Herbicide label for wheat and barley and a PBI of 30 days will be required for all other crops not listed on the label. With the implementation of these PBIs, maximum residue limits (MRLs) will not be required for residues of pinoxaden and the metabolites M2 and M3 in secondary crops.

Figure 2 **Proposed Metabolic Profile of Pinoxaden in Rotational Wheat, Radish, Turnip, Lettuce and Mustard**



4.3 Nature of the Residue in Animals

Lactating Goat

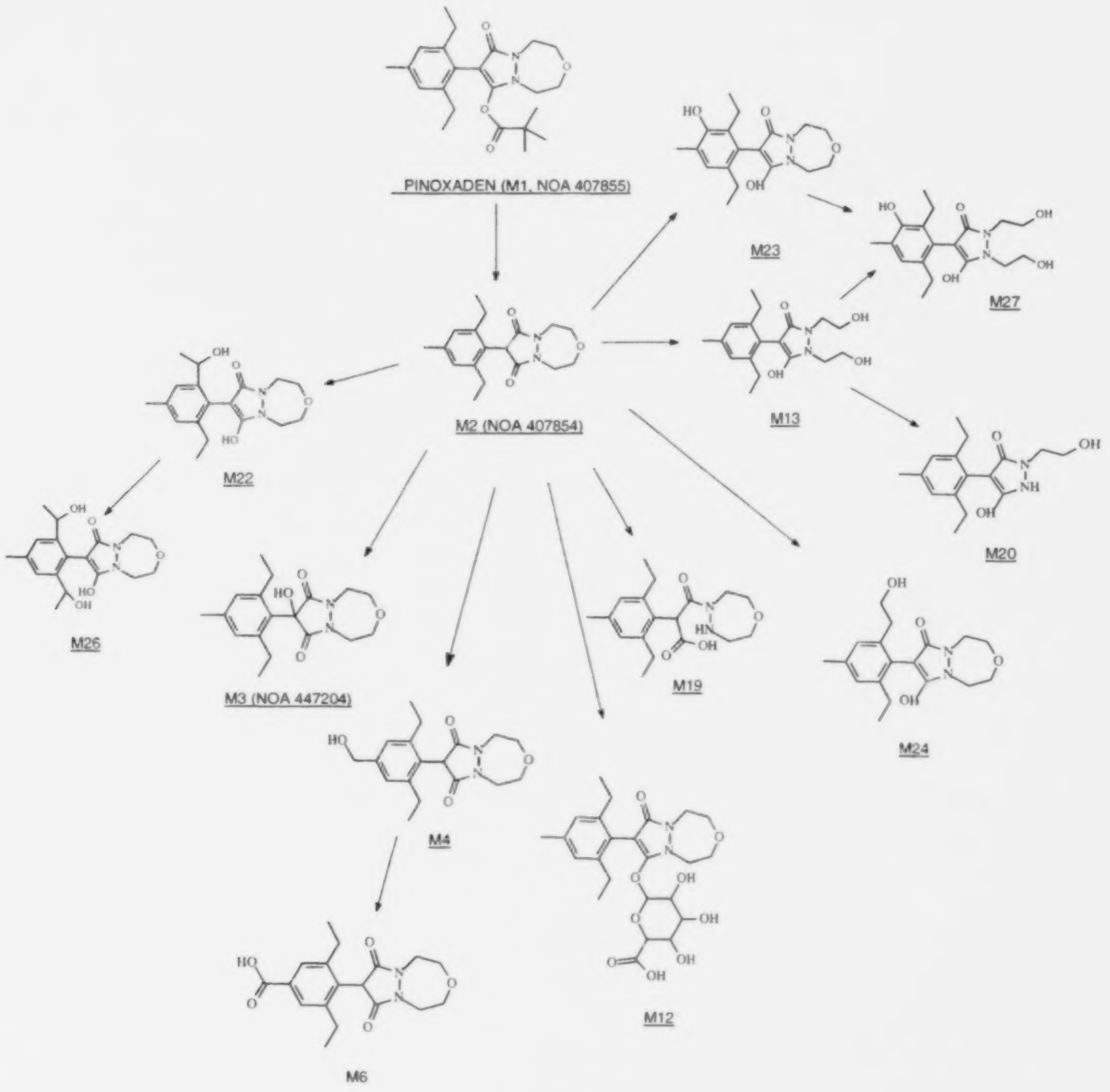
Two goat metabolism studies were performed; the first one was carried out with the parent compound, pinoxaden, and the second one with a predominant plant metabolite, M4. In the first study, pinoxaden (phenyl radiolabel) was administered orally to two lactating goats (*Capra hircus*, Alpine breed) at dose levels of 120.6 ppm (mg/kg feed/day) for four consecutive days. Approximately 83% of the administered dose (AD) was eliminated in excreta (feces, urine, gastrointestinal tract and rumen), 0.009% of the AD was transferred to milk and 0.260% of the AD was recovered in tissues, demonstrating low tissue burden. The highest concentrations of ^{14}C-residues were detected in kidney (2.953 ppm) and liver (1.160 ppm). The parent compound, pinoxaden, was not detected in any of the matrices, indicating its rapid and complete metabolism in the lactating goat. The predominant metabolite detected in all the goat matrices was M2, which is the hydrolysis product of the parent molecule pinoxaden. Several minor metabolites (M3, M4, M6, M12, M13, M19, M20, M22, M23, M24, M26, M27 and M28), each representing less than 10% TRRs, were detected in feces and in some tissues and milk.

In the second study, metabolite M4 was administered orally to two lactating goats (*Capra hircus*, Alpine breed) at dose levels of 9.8 ppm (mg/kg feed/day) for four consecutive days. Approximately 93% of the AD was eliminated in excreta (feces, urine, gastrointestinal tract and rumen). ^{14}C-residues in milk, muscle, fat and blood were below the LOQ (0.002 ppm in milk and 0.011 ppm in tissues). Only minor fractions of the total AD were transferred to the remaining tissues (<0.1% of the AD). The highest concentrations of ^{14}C-residues were detected in kidney (0.044 ppm) and liver (0.025 ppm). The predominant metabolite, identified in all tissues containing detectable residues, was unchanged M4. The only other metabolite identified was M10, which is the hydroxylation product of M4. M10 represented only a minor fraction of the TRRs in liver and kidney, and represented less than 10% of TRRs in feces.

These results indicate that residues of pinoxaden and the major plant metabolite M4 (and by inference all metabolites sharing a similar structure) have a very low transfer into the edible tissues and milk of lactating goats.

Based on the findings of the lactating goat metabolism studies, the ROC in ruminant tissues and milk for risk assessment and enforcement purposes was defined as pinoxaden (as M2) and metabolites M2 and M4 (free and conjugate).

Figure 3 Proposed Metabolic Profile of [Phenyl - 1- ^{14}C]Pinoxaden in Lactating Goat



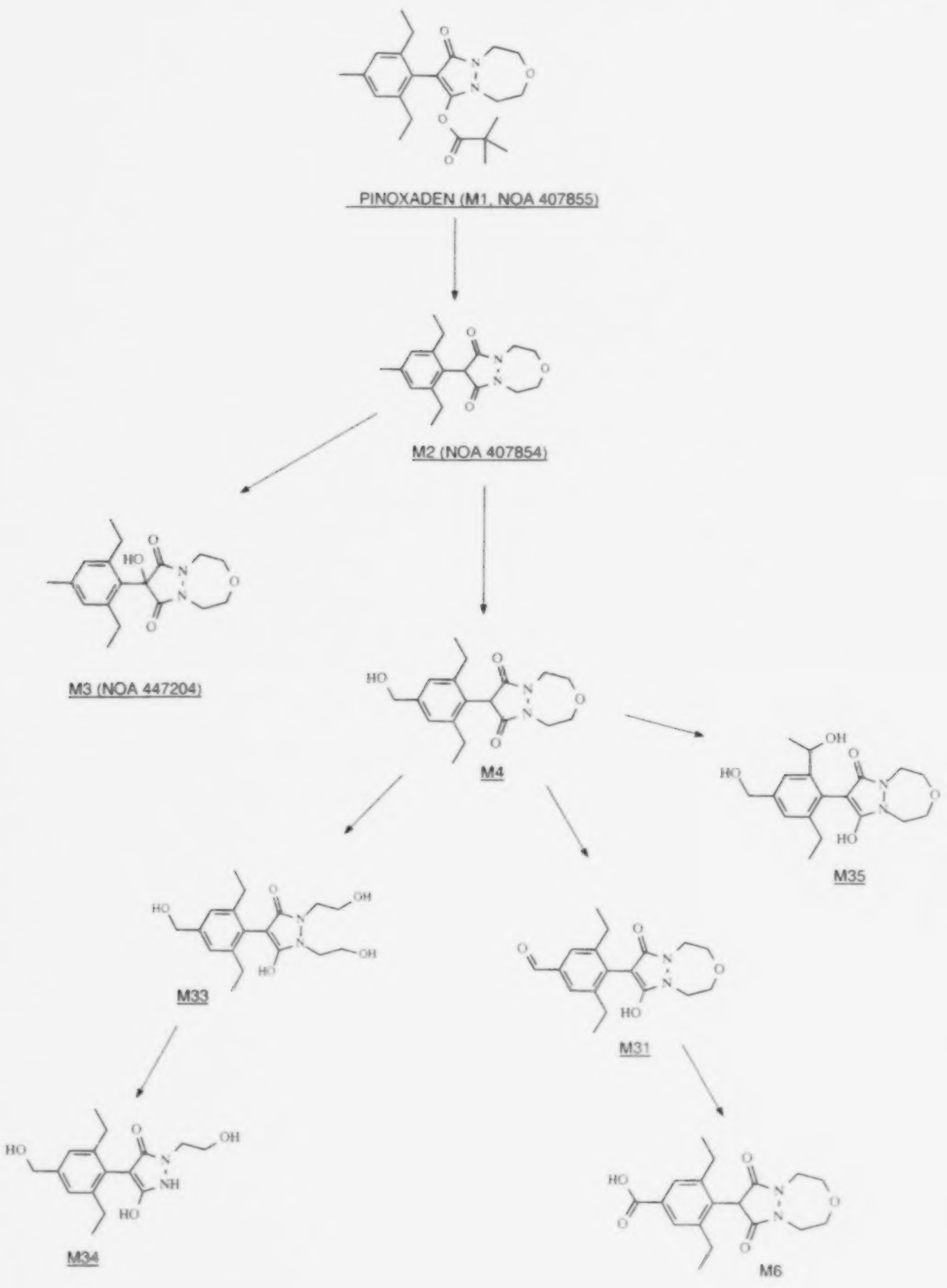
Laying Hen

Pinoxaden (phenyl radiolabel) was administered orally to five laying hen (*Gallus gallus domesticus*, White Leghorn Hyline W-98 Breed) at dose levels of 96.7 ppm (mg/kg feed/day) for four consecutive days. Approximately 75% of the AD was eliminated in excreta, with an additional 10% of the AD recovered in the gizzard. Only minor fractions of the total AD were transferred to eggs (0.007%) and edible tissues (0.158%). The highest concentrations of ^{14}C-residues were detected in kidney (1.782 ppm) and liver (0.617 ppm). The parent compound, pinoxaden, was not detected in any of the matrices, indicating its rapid and complete metabolism in the laying hen. The major metabolites detected in all the hen matrices were M2, M4 and M6. Minor metabolites (<10% of the TRRs) identified in excreta, eggs and some tissues were M31, M33, M34 and M35.

Based on the findings of the laying hen metabolism study, the ROC in poultry tissues and eggs for risk assessment and enforcement purposes was defined as pinoxaden (as M2) and the metabolites M2, M4 (free and conjugate) and M6.

The metabolism of pinoxaden in animal is well understood. The metabolic profile of pinoxaden in the dairy cow and the laying hen was very similar to that in the rat. In the rat, pinoxaden was rapidly absorbed, extensively metabolized and highly excreted. No parent was detected in excreta. The metabolism of pinoxaden appeared to proceed via hydrolysis of the ester moiety to form M2, which was then metabolized to form a wide variety of minor metabolites including M4. Similarly, the main route of metabolism of pinoxaden in cattle and hen was predominantly via the hydrolysis of the ester moiety of the parent compound to form the metabolite M2. Minimal transfer to muscle, milk, egg and fat was observed.

Figure 4 Proposed Metabolic Profile of Pinoxaden in Laying Hen



4.4 Methods for Residue Analysis of Plants and Plant Products

Two HPLC-MS/MS methods (REM 199.02 and REM 199.03) were proposed for data-gathering purposes for the analysis of pinoxaden residues (as M2) as well as metabolites M2, M4, M6 and M10 in cereal matrices. Briefly, homogenized samples were extracted with 1N HCl under reflux for two hours. With Method REM 199.02, following filtration (if necessary), the pH of the extract was raised with 3% ammonia solution and analysis was performed by reversed-phase HPLC-MS/MS (column-switching; two analytical sequences with different chromatographic conditions were necessary to quantify the four analytes). With Method REM 199.03, following the addition of the ammonia solution, the extract was filtered using a Vectaspin filtration tube and was cleaned up onto an Oasis HBL SPE cartridge. Analysis was performed by HPLC-MS/MS.

Method 117-01, the proposed enforcement method, involved extracting homogenized samples with 1N HCl (or 1N HCl/acetonitrile [90:10, v/v]) under reflux for two hours. For determination of combined residues of pinoxaden and M2 (as M2), an aliquot of the extract was filtered (if the solution was not clear) and, after dilution with water, the final fraction was injected onto a reversed-phase C_{18} to ODS-3 two-column switching HPLC-MS/MS system for analysis. For determination of M4 and M6, an aliquot of the extract was filtered (if the solution was not clear), and the extract was cleaned up with a preconditioned SCX (2) SPE cartridge. The purified extract was then evaporated to an aqueous solution and the concentrated sample was loaded onto a preconditioned C_8 SPE cartridge. The eluate was evaporated to an aqueous solution and, after dilution with 0.2% formic acid, the final fraction was injected onto a SCX to C_8 two-column switching HPLC-MS/MS system for analysis.

The LOQ for each analyte for the three methods were reported as 0.01 ppm in cereal grain and as 0.02 ppm in cereal forage, hay and straw. These methods were found to give recoveries within the acceptable range of 70–120% for the analysis of cereal matrices (whole plant, forage, grain, hay and straw). The independent laboratory validation supported the reliability and reproducibility of the Method 117-01 for the determination of pinoxaden as well as metabolites M2, M4 and M6 in cereal matrices. The extraction efficiency conducted with wheat samples collected from the metabolism studies indicated that the HPLC-MS/MS method 117-01 adequately extracted bioincurred residues of M2, M4, M6 and M10 from wheat matrices.

Therefore, Method 117-01 is valid as a data-gathering method and enforcement method for the determination of pinoxaden and the metabolites M2, M4 and M6 in plant matrices.

4.5 Methods for Residue Analysis of Food of Animal Origin

A HPLC-MS/MS method (Method T001530-03) was proposed for data-gathering and enforcement purposes for the determination of two major pinoxaden metabolites M4 and M6. Briefly, samples were refluxed with 1N HCl for two hours to extract the residues. An aliquot of the filtered extract was passed through a preconditioned SCX (2) SPE column for clean-up. The eluate and the acetonitrile/water (25:75, v/v) rinse were combined and evaporated to an aqueous solution by rotary evaporation. The aqueous solution was loaded onto a preconditioned C_8 SPE column. The eluate was evaporated to an aqueous solution by rotary evaporation. The final volume was adjusted with 0.2% formic acid, and aliquots were measured directly by injection into an HPLC-MS/MS system for analysis.

The LOQ for each analyte was reported as 0.01 ppm for milk and as 0.02 ppm for tissues and eggs. This method was found to give acceptable recoveries for the analysis of livestock matrices (in milk, recoveries ranging from 87% to 100% for M4 [coefficient of variation of 12%] and 98% to 108% for M6 [coefficient of variation of 5%] when spiked at the LOQ and in tissues, ranging from 81% to 104% [coefficient of variation of 2% to 8%] for M4 and 80% to 105% for M6 [coefficient of variation of 2% to 8%]). The independent laboratory validation supported the reliability and reproducibility of Method T001530-03 for the determination of M4 and M6 in beef muscle, beef fat, milk and eggs. The registrant submitted a scientifically acceptable rationale to waive the requirement of a radio-validation study for this method. Method T001530-03 is considered acceptable as a data-gathering method for the determination of M4 and M6 in livestock matrices.

However, to be considered as the enforcement method in livestock matrices, Method T001530-03 must analyze for all the components of the ROC. The ROC in ruminant was defined as pinoxaden (as M2), M2 and M4 (free and conjugate) and in poultry as pinoxaden (as M2), M2, M4 (free and conjugate) and M6.

4.6 Storage Stability Data—Plant/Animals

Wheat Matrices

The data presented in the freezer storage stability study indicated that residues of M2, M4, M6 and M10 were stable at ≤-18°C for 15 months in wheat whole plant, straw and grain.

Livestock Matrices

The data presented in the freezer storage stability study indicated that residues of M4 and M6 were stable at -20°C for up to 3 months in chicken muscle, beef liver, milk and eggs.

Only freezer storage stability of the metabolites M4 and M6 in livestock matrices was demonstrated. According to the wheat metabolism studies, pinoxaden was completely and rapidly converted to M2 and subsequently M4 (predominant metabolite) in livestock feed items. Therefore, the transfer of measurable residues (>LOQ) of pinoxaden and metabolite M2 (components of the ROC) to meat, milk and eggs is not expected, as supported by the livestock metabolism studies. As such, the freezer storage stability of pinoxaden and M2 in livestock matrices is not required for the purposes of this submission.

Processed Commodities

No freezer storage stability data for residues of pinoxaden (as M2), M2, M4 and M6 in wheat processed fractions (aspirated grain fraction, bran, flour, middling, shorts and germ) and in barley processed fractions (bran, flour and pearled barley) were submitted. Such data are required in order to validate the processing studies.

4.7 Crop Field Trials

Wheat
Supervised crop field trials in wheat were conducted throughout the wheat growing regions of the United States and Canada. In the American trials, wheat was treated with NOA 407855 100EC or NOA 407855 120EC at a rate of 72.5 g a.i./ha. In the Canadian trials, wheat was treated with one of the three following formulations at a rate of 70 g a.i./ha: 100EC Lead Variant, 100EC Alternate Variant or 120EC Aromatic 200. A safener (cloquintocet-mexyl) and an adjuvant were added to the spray mixture for all applications. The results from the American trials showed that the maximum combined residues of pinoxaden (M2 + M4 + M6) were 0.95 ppm in wheat spring forage (PHI of 30 days), 3.07 ppm in wheat fall forage (PHI of 30 days), 1.71 ppm in wheat hay (PHI of 30 days), 1.49 ppm in wheat straw (PHI of 60 days) and 0.72 ppm in wheat grain (PHI of 60 days). The results from the Canadian trials showed that the maximum combined residues of pinoxaden (M2 + M4 + M6) were 3.75 ppm in wheat forage (PHI of 6 to 8 days), 0.92 ppm in wheat hay (PHI of 28 to 36 days), 0.19 ppm in wheat straw (PHI of 58 to 72 days) and 0.08 ppm in wheat grain (PHI of 58 to 72 days). Residue decline studies in wheat demonstrated that the proposed MRL for wheat grain will not be exceeded when collected at a PHI of 60 days. The proposed MRL of 1.3 ppm to cover residues of pinoxaden (as M2), M2, M4 (free and conjugate) and M6 in/on wheat grain was calculated using the MRL Statistical Methodology (Excel® spreadsheet) developed by the NAFTA Tolerance/MRL Harmonization Workgroup.

Barley
Supervised crop field trials in barley were conducted throughout the barley growing regions of the United States and Canada. In the American trials, barley was treated with Pinoxaden 100EC or NOA 407855 120EC at a rate of 72.5 g a.i./ha. In the Canadian trials, barley was treated with one of the three following formulations at a rate of 70 g a.i./ha: 100EC Lead Variant, 100EC Alternate Variant or 120EC Aromatic 200. A safener (cloquintocet-mexyl) and an adjuvant were added to the spray mixture for all applications. The results from the American trials showed that the maximum combined residues of pinoxaden (M2 + M4 + M6) were 1.10 ppm in barley hay (PHI of 30 days), 0.62 ppm in barley straw (PHI of 60 days) and 0.69 ppm in barley grain (PHI of 60 days). The results from the Canadian trials showed that the maximum combined residues of pinoxaden (M2 + M4 + M6) were 0.77 ppm in barley hay (PHI of 26 to 36 days), 0.22 ppm in barley straw (PHI of 54 to 70 days) and 0.16 ppm in barley grain (PHI of 54 to 70 days). Residue decline studies in barley demonstrated that the proposed MRL for barley grain will not be exceeded when collected at a PHI of 60 days. The proposed MRL of 0.9 ppm to cover residues of pinoxaden (as M2), M2, M4 (free and conjugate) and M6 in/on barley grain was also calculated using the MRL Statistical Methodology (Excel® spreadsheet) developed by the NAFTA Tolerance/MRL Harmonization Workgroup.

4.8 Processed Food/Feed

Wheat
Pinoxaden (100EC formulation) was applied to wheat plants at either 70 g a.i./ha or 365 g a.i./ha. The wheat grains were harvested 60 days after treatment and processed into aspirated grain fraction, bran, flour, middling, shorts and germ. A comparison of the residues in the raw

agricultural commodity with those in each processed fraction resulted in average concentration factors of 0.2× for wheat aspirated grain fraction, 0.2× for wheat flour, 0.7× for wheat middling, 1× for wheat shorts and 0.7× for wheat germ. In wheat bran, the concentration factors observed were very different between the 2 trials, amounting to 1.4× (70 g a.i./ha) and to 4.6× (365 g a.i./ha). An MRL of 3.0 ppm will be established to cover residues of pinoxaden (as M2), M2, M4 (free and conjugate) and M6 in wheat bran.

Barley

Pinoxaden (100EC formulation) was applied to barley plants at either 70 g a.i./ha or 365 g a.i./ha. The barley grains were harvested 60 days after treatment and processed into bran, flour and pearled barley. A comparison of the residues in the raw agricultural commodity with those in each processed fraction resulted in average concentration factors of 0.42× for barley flour and of 0.99× for pearled barley. In barley bran, the concentration factors observed were very different between the two trials, amounting to 2.43× (70 g a.i./ha) and to 0.82× (365 g a.i./ha). An MRL of 1.6 ppm will be established to cover residues of pinoxaden (as M2), M2, M4 (free and conjugate) and M6 in barley bran.

Upon receiving the freezer storage stability data for metabolites M2, M4 and M6 in cereal processed commodities, the validity of the processing studies and of the proposed MRLs for wheat and barley bran will be assessed.

4.9 Meat/Milk/Poultry/Eggs

Dairy Cattle

Lactating Holstein cattle were orally administered by gelatin capsule 1, 3 or 10 mg of metabolite M4 per kilogram of feed per day for 29 or 30 consecutive days. Cows were milked twice daily and tissue samples (liver, kidney, muscle and fat) were collected 20 to 24 hours after the last dose. No quantifiable residues of either M4 or M6 were observed in milk (<0.01 ppm) and tissues (<0.02 ppm) from animals treated at the highest dose (10 ppm). The expected meat, meat by-products and milk residues resulting from the feeding of treated crops are 0.04 ppm, 0.04 ppm and 0.02 ppm, respectively.

The calculation of the maximum theoretical dietary burden took into account a diet consisting of a mixture of wheat (forage, hay, grain and straw) and barley (hay, straw and grain) feed items. Using the maximum residues observed in Canadian field trials, the maximum theoretical dietary burden was calculated to be 5.4 ppm for beef cattle and 9.0 ppm for dairy cattle. At the 10 ppm feeding level (~1× the maximum theoretical dietary burden), the residues in all cow matrices were below the combined LOQs (0.02 ppm in milk and 0.04 ppm in tissues) for both metabolites. Should additional uses be proposed for pinoxaden in the future that may result in an increase of the maximum theoretical dietary burden, an additional feeding study may be required.

Laying Hen

Laying White Leghorn hens were orally administered by treated feed 0.5, 1.5 or 5 mg of metabolite M4 per kilogram of feed per day for 28 consecutive days. Eggs were collected twice daily and tissue samples (skin with attached fat, peritoneal fat, liver, breast muscle and thigh muscle) were collected 20 to 24 hours after the last dose. No quantifiable residues of either M4 or M6 were observed in egg and tissue (<0.02 ppm) samples across all dose groups. The expected meat, meat by-products and egg residues resulting from the feeding of treated crops are 0.06 ppm, 0.06 ppm and 0.06 ppm, respectively.

The calculation of the maximum theoretical dietary burden took into account a diet consisting entirely of wheat grain, wheat milled by-product and barley grain. Using the maximum residues observed in Canadian field trials, the maximum theoretical dietary burden was calculated to be 1.5 ppm. At the 1.5 ppm feeding level (1× the maximum theoretical dietary burden), the residues in all hen matrices were below the LOQ (0.02 ppm for eggs and tissues) for each metabolite.

4.10 Dietary Risk Assessment

The proposed domestic use of pinoxaden on wheat and barley does not pose an unacceptable chronic or acute dietary (both food and water) risk to any segment of the population, including infants, children, adults and seniors.

5.0 Fate and Behaviour in the Environment

5.1 Physical and Chemical Properties Relevant to the Environment

A summary of the available physical-chemical properties and molecular structure of, pinoxaden and the major transformation products, M2 and M3, are provided in Appendix III, Table 1 to 3.

Pinoxaden

The high solubility (200 mg/L) in water is one of the indicators of a potential for leaching. The vapour pressure is 4.6×10^{-12} atm and the Henry's law constant is $K = 9.09 \times 10^{-12}$ atm m^3/mole ($1/H = 1.1 \times 10^6$). These values indicate that pinoxaden is not likely to volatilize under field conditions and from water or moist soil surfaces. Pinoxaden does not absorb light at wavelengths above 287 nm, indicating that there is limited potential for phototransformation. There is no p*K*a in the pH range of 1.1–12.0, indicating that pinoxaden does not dissociate in water. The log K_{ow} is 3.2, which triggers a bioaccumulation study with pinoxaden.

M2

The high solubility (5.2–300 g/L) in water is one of the indicators of a potential for leaching. The vapour pressure is 5.2×10^{-13} atm and the Henry's law constant is $K = 3.2 \times 10^{-14}$ to 5.4×10^{-16} atm m^3/mole ($1/H = 4.5 \times 10^{13}$). These values indicate that M2 is not likely to volatilize under field conditions and from water or moist soil surfaces. There was no data provided regarding absorption of light. The p*K*a for M2 is 3.82. The log K_{ow} is 0.62–1.7 indicating that there is little potential for M2 to bioaccumulate.

M3

The high solubility (370 mg/L) in water is one of the indicators of a potential for leaching. The vapour pressure is 3.2×10^{-12} atm and the Henry's law constant is $K = 3.2 \times 10^{-12}$ atm m^3/mole ($1/H = 7.7 \times 10^9$). These values indicate that M3 is not likely to volatilize under field conditions and from water or moist soil surfaces. There was no data provided regarding absorption of light. There is no p*K*a found, indicating that M3 does not dissociate in water. The log K_{ow} is 1.8 indicating that there is little potential for M3 to bioaccumulate.

ADIGOR Adjuvant

The major components of ADIGOR Adjuvant (A12127S formulation) are fatty acids (rapeseed methyl esters), which are hydrophobic in nature. Solubility of the major components in water ranges from 3.4×10^{-12} to 1.1×10^{-9} g/L. Plant fatty acids form globules rather than slicks when added to water. In the UV–visible spectrum there was no absorption observed between 340 and 750 nm; however, there was some absorption at 296 nm (14 L/mol · cm). Based on the UV–visible spectrum, these compound are not expected to phototransform. The vapour pressures for the main components range from 5.86×10^{-4} to 1.14×10^{-3} Pa and the Henry's law constants range from 3.6 Pa m^3/mol to 580 Pa m^3/mol at 25°C. Thus, these compounds are expected to volatilize from dry and moist surfaces and water. The log K_{ow} values for these components range from 6.29 to 8.35. These values generally would trigger the requirement for a bioaccumulation study. The components of methylated rapeseed oil have no acidic or basic functions and are not expected to dissociate. The ADIGOR Adjuvant formulation to be used in Canada (A12127S) differs slightly from the formulation currently registered in the European Union (A12127R); however, these two products are sufficiently similar to allow studies conducted with A12127R to be submitted for review of the Canadian formulation of ADIGOR Adjuvant (A12127S formulation).

5.2 Abiotic Transformation

Hydrolysis is expected to be a route of transformation for pinoxaden and for M3 at high pH values. At 25°C, hydrolysis of pinoxaden was dependent on pH, with a half-life of 17.5 days at pH 5 and of 0.21 days at pH 9. Transformation product M2 was found to be stable to hydrolysis. The half-lives of M3 were stable, 57 days and 15 hours at pH 5, pH 7 and pH 9, respectively. At 15°C, the pinoxaden half-lives were 23.7 days at pH 7 and 0.7 day at pH 9 (pH 5 was not tested, but the half-life is expected to be greater than 30 days).

Phototransformation is not expected to be an important transformation route for pinoxaden on soils. The rates of transformation in irradiated samples were slower than in dark controls; therefore, a phototransformation half-life is not appropriate. The M2 soil phototransformation half-life was calculated to be 19.8 days. A minor transformation product, NOA 437397, was identified; however, the concentrations of this product increased to 6.7% of the applied radioactivity at study termination. There is a possibility that, given more time, this compound would reach 10% of the applied radioactivity. Phototransformation is expected to be a route of transformation for pinoxaden in the photic zone of aquatic systems. Half-lives for pinoxaden in sterile water were 7.9 and 9.8 days (30–50°N and 60°N, respectively). The major transformation product detected was M2, which had half-lives of 8.1 and 10.1 days (30–50°N and 60°N, respectively). It was not possible to determine the photolytic half-lives of M3 from the data submitted.

Based on data available in the literature, the ADIGOR Adjuvant (A12127S formulation) mixture is predicted to have a hydrolysis half-life of less than 10 days. The primary constituent, methylated rapeseed oil, is expected to be photochemically stable.

5.3 Biotransformation

The biotransformation of pinoxaden and transformation product M2 was rapid in aerobic soils. In loamy sand, the dissipation time 50% (DT_{50}) under laboratory conditions for all three radiolabels of pinoxaden ranged from 0.2 to 0.5 days; however, these values are were likely influenced by hydrolysis at the high soil pH level in the studies (pH 7.7). For M2, the DT_{50} ranged from 3.8 to 7.1 days. M3 was the most persistent compound, with a half-lives ranging from 48 to 96 days. In aerobic soils, pinoxaden and M2 are classified as non-persistent and M3 as moderately persistent, according to the classification scheme of Goring et al. (1975).

Following introduction into an aerobic water system with sandy loam and silty clay loam sediments, pinoxaden underwent biotransformation to M2 and M3. M2 reached a maximum concentration of 26.9% of the applied radioactivity (silty clay loam) in sediment. Pinoxaden disappeared rapidly from aerobic water systems with no detections after three days in the water or sediment. The DT_{50} values for pinoxaden in an aerobic water system was less than one day. Hydrolysis is expected to have contributed to loss of test material in the water column, as the half-lives observed for pinoxaden in aerobic water were similar to those seen in the hydrolysis study at pH 9 (this study was conducted at pH 8.3). Pinoxaden is classified as non-persistent in aerobic aquatic environments and M2 would be calculated as non-persistent to slightly persistent according to the classification scheme of McEwen and Stephenson (1979).

Following introduction into anaerobic water systems with sand, sandy loam and silty clay loam sediments, pinoxaden underwent biotransformation to M2 and M3. M2 reached maximum concentrations of 22.9, 16.5 and 26.9% of the applied radioactivity in sediment in the European pond, European river and American pond, respectively. However, the log K_{ow} (1.7) and solubility (5200–300 000 mg/L) for M2 appears counter to the reported concentrations of this compound in sediment (26.9% of the applied). This raises the question of precipitate formation during the study, or it may be, that M2 was associated with pore water that was not adequately separated from the sediment prior to analysis. Pinoxaden disappeared rapidly from anaerobic water systems with no detections by three days in the water or sediment. The DT_{50} value for pinoxaden in an anaerobic water system was less than one day. Hydrolysis is expected to have contributed to loss of test material in the water column, as the dissipation times observed for pinoxaden in anaerobic water were similar to those seen in the hydrolysis study at pH 9 (this study was conducted at pH 8.3). Pinoxaden is expected to be non-persistent in anaerobic aquatic systems, and M2 is expected to be non-persistent to slightly persistent in anaerobic aquatic systems based on McEwen and Stephenson (1979).

There is limited information on the biotransformation of ADIGOR Adjuvant (A12127S formulation) in soils or water. The primary constituent, methylated rapeseed oil, is expected to biotransform in aerobic soil and aqueous systems with half-lives in the order of seven days and, therefore, is non-persistent.

5.4 Mobility

The adsorptive and desorptive characteristics of pinoxaden, M2 and M3 were studied in five soils (loamy sand, two loams, sand and a silty clay loam). The K_d values for pinoxaden were 4.9, 13.4, 1.0, 11.0 and 8.9 in loamy sand, loam (North Dakota), sand, loam (Manitoba) and silty clay loam, respectively. The corresponding organic carbon adsorption coefficient (K_{oc}) values were 403, 453, 299, 337 and 852. Based on the K_{oc} values and the mobility classification scheme of McCall et al. (1981), pinoxaden is expected to exhibit low to moderate mobility in a variety of soils. It was not possible to determine if there were correlations between adsorption and any soil parameters.

The K_d values for M2 were 0.06, 0.18, 0.08, 0.14 and 0.28 in loamy sand, loam (North Dakota), sand, loam (Manitoba) and silty clay loam, respectively. The corresponding adsorption K_{oc} values were 5.2, 6.0, 23, 4.2 and 27. Based on K_{oc} values and the classification of McCall et al. (1981), M2 is expected to exhibit very high mobility in a variety of soils.

The K_d values for M3 were 0.28, 0.76, 0.12, 0.86 and 0.5 in loamy sand, loam (North Dakota), sand, loam (Manitoba) and silty clay loam, respectively. The corresponding adsorption K_{oc} values were 23, 26, 35, 26 and 48. Based on K_{oc} values and the classification of McCall et al. (1981), M2 is expected to exhibit very high mobility in a variety of soils.

The compounds in the ADIGOR Adjuvant (A12127S formulation) mixture are expected to adsorb to soils and have limited leaching potential. Some of the shorter chain fatty acids, however, may leach to depth.

5.5 Dissipation and Accumulation under Field Conditions

Based on the results of the field dissipation trials, neither the parent compound, pinoxaden, nor the transformation product, M2, are expected to carry-over to the following growing season. Transformation product M3 is expected to carry-over (16.1, 5.3 and 14.8% of applied parent in Manitoba, Saskatchewan and Alberta, respectively) into the following growing season. Application of NOA 407855 120 EC to bare field test plots at rates in excess of 110% of the proposed Canadian maximum rate (0.06 kg a.i./ha) resulted in DT_{50} values for pinoxaden of 2, 5, 2 and 3 days in Manitoba, Saskatchewan, Alberta and North Dakota, respectively, and corresponding DT_{90} values of 7, 18, 6 and 11 days. The DT_{50} values for M2 were 2, 16, 15 and 5 days in Manitoba, Saskatchewan, Alberta and North Dakota, respectively, with corresponding DT_{90} values of 8, 53, 50.5 and 16 days. For M3, DT_{50} values were 315, 176 and 161 days in Manitoba, Saskatchewan and North Dakota, respectively, with corresponding DT_{90} values of 1047, 570.5 and 536 days. M3 DT_{50} and DT_{90} values could not be calculated from the Alberta data.

Pinoxaden and M2 were detected almost entirely in the 0- to 10-cm soil depth and were not detected below 25 cm depth. M3, however, was detected to depths of 25 cm at all sites. M3 was also was detected to a depth of 45 cm at the Alberta site and 60 cm at the Washington site. The greatest leaching was found under the two extreme sites, Alberta (drought conditions) and Washington (excessive irrigation). Thus, leaching of M3 is expected.

5.6 Bioaccumulation

The applicant submitted a waiver with respect to bioaccumulation of pinoxaden. Although a log K_{ow} of 3.2 indicates that there is a potential for bioaccumulation of pinoxaden, exposure to pinoxaden in the aquatic environment is expected to be limited based on the aquatic biotransformation DT_{50} values of <1 day. Therefore, pinoxaden bioconcentration/bioaccumulation is unlikely. The log K_{ow} of M2 is 1.7; therefore, it is unlikely that M2 will bioconcentration/bioaccumulate. No studies were submitted for ADIGOR Adjuvant (A12127S formulation).

5.7 Summary of Fate and Behaviour in the Terrestrial Environment

Laboratory studies of transformation in soil indicate that biotransformation will most likely be the major route of transformation for pinoxaden in aerobic soils. However, these studies were conducted at high pH values and, thus, the observed rates were likely strongly influenced by hydrolysis. The half-lives of pinoxaden in acid soils where hydrolysis is not a significant factor are also expected to be short, based on the terrestrial field dissipation results for Saskatchewan and Alberta (soil values of pH 5.8 and pH 6.4). Photolysis is not an important route of transformation in soil. The low vapour pressure (4.6×10^{-12} atm) and Henry's law constant ($1/H = 1.1 \times 10^{6}$) indicate that pinoxaden is non-volatile from dry soil and water or moist soils.

Under aerobic soil conditions, pinoxaden was non-persistent in sandy loam soils with DT_{50} values ranging from 0.2–0.3 days. The major transformation products formed were M2 and M3. Minor transformation products included unidentified polar compounds. Aerobic soil biotransformation studies with the transformation products found M2 to be non-persistent (DT_{50} values of 3.8–7.1 days) and M3 to be moderately persistent (half-lives of 48–96 days).

Pinoxaden and its transformation products are expected to be mobile in soils. Adsorption/desorption studies in a variety of soils indicate low to moderate mobility for pinoxaden and very high mobility for M2 and M3.

The field dissipation studies conducted in Manitoba, Saskatchewan, Alberta and North Dakota also indicate rapid dissipation of pinoxaden and M2, with DT_{50} values ranging from 2 to 5 days for pinoxaden and 2 to 16 days for M2. M3 was found to be moderately persistent to persistent based on the classification of Goring et al. (1975) with DT_{50} values of 161–315 days. Therefore, pinoxaden residues (as M3) are expected to carry over (5.3–16.1% of applied parent) to the start of the following growing season (i.e., spring).

Biotransformation of pinoxaden is expected to be the major route of transformation in aerobic soil (half-life seven days). Transformation in aerobic aquatic systems is expected, although a half-life was not calculated. The estimated half-life in aquatic systems is seven days; therefore, pinoxaden is non-persistent based on the classification of Goring et al. (1975).

5.8 Summary of Fate and Behaviour in the Aquatic Environment

Pinoxaden may reach the aquatic environment as a result of off-target spray drift or via overland run-off during rainfall events under the right field conditions. Based on the mobility of pinoxaden (low to moderate) as well as transformation products M2 (very high) and M3 (very high), there is a potential for leaching to groundwater and subsequent recharge of surface water. However, due to pinoxaden's short half-life (0.2–0.3 days in soil), it is not expected to be of concern.

Pinoxaden may undergo photolytic conversion in clear surface waters (half-life of 14 to 21 days); however, this is not a major route of transformation. Hydrolysis is expected to contribute significantly to the transformation of pinoxaden in alkaline surface waters (e.g., pH 8). Of the transformation products, M2 is stable to hydrolysis, and M3 has half-lives of 0.6 and 57 days at pH 9 and pH 7, respectively.

Aerobic and anaerobic aquatic system laboratory studies indicate that once pinoxaden enters the aquatic environment it will rapidly transformation to M2 and M3. In sediment, only M2 was detected at concentrations greater than 3% of applied radioactivity, with a maximum concentration of 26.9% (applied radioactivity) in a silty clay loam sediment. Under aerobic and anaerobic conditions, pinoxaden is non-persistent in water (DT_{50} values of <1 day). However, these results were all determined in studies conducted at higher pHs (water pH 8.1–8.3), where hydrolysis is a major route of transformation ($t_{1/2} = 0.9$ days). Therefore, under acid or neutral conditions, pinoxaden is expected to persist longer than reported. However, pinoxaden is still classified to be non-persistent according to McEwen and Stephenson (1979) under these conditions.

The major transformation product is M2 with minor amounts of M3. M2 is non-persistent in water (maximum DT_{50} values of 14 days) under aerobic conditions and non-persistent to slightly persistent in water (DT_{50} values of 15 hours–20.6 days) under anaerobic conditions.

Although a log K_{ow} of 3.2 indicates that there is a potential for bioaccumulation of pinoxaden, exposure to pinoxaden in the aquatic environment is expected to be limited based on the aquatic biotransformation DT_{50} values of <1 day. Therefore, pinoxaden bioconcentration/ bioaccumulation is unlikely. The log K_{ow} of M2 is 1.7; therefore, it is unlikely that M2 will bioconcentrate/bioaccumulate.

The transformation of fatty acids in ADIGOR Adjuvant (A12127S formulation) is expected to be the major route of transformation in aquatic systems (aerobic aquatic half-life 7 days); therefore, ADIGOR is non-persistent according to McEwen and Stephenson, 1979.

5.9 Expected Environmental Concentrations

5.9.1 Soil

The expected environmental concentration (EEC) in soil for the direct overspray of pinoxaden at 60 g a.i./ha is 0.027 mg a.i./kg dw soil, as determined on the basis of a bulk density of 1.5 g/cm^3

and a soil depth of 15 cm. The EECs for M2 and M3 are estimated to be 100% of the pinoxaden EEC. The EEC in soil for the direct overspray of AXIAL 100EC Herbicide is 0.27 mg EP/kg dw soil, as determined on the basis of a bulk density of 1.5 g/cm^3 and a soil depth of 15 cm. For ADIGOR Adjuvant (A12127S formulation), the EEC for direct overspray application at the maximum rate (645.5 g/ha), assuming soil bulk density of 1.5 g/cm^3 and soil depth of 15 cm, is 0.29 mg/kg soil.

5.9.2 Aquatic Systems

Direct Overspray in Surface Water

The expected environmental concentration (EEC) in surface waters for the direct overspray of pinoxaden at 60 g a.i./ha to a water depth of 30 cm is 0.02 mg a.i./L. The EECs for M2 and M3 are estimated to be 100% of the pinoxaden EEC based on rapid transformation. The EEC for the end-use product, based on an application rate of 618 g EP/ha, was 0.206 g EP/L. The EEC for ADIGOR Adjuvant (A12127S formulation) for the agricultural direct overspray scenario for surface waters at water depth of 30 cm is 0.22 mg/L.

Drinking Water

EECs of pinoxaden and two transformation products in potential drinking water sources (groundwater and surface water) were estimated using computer simulation models. An overview of how EECs are estimated is provided in the PMRA's Science Policy Notice SPN2004-01, *Estimating the Water Component of a Dietary Exposure Assessment*. EECs of pinoxaden and its transformation products in groundwater were calculated using the Leaching Estimation and Chemistry Model (LEACHM), which simulates leaching through a layered soil profile over a multi-year period (20 years). The concentrations calculated using LEACHM are estimates of the flux, or movement, of pesticide into shallow groundwater (2-m or 5-m depth) with time. EECs of pinoxaden and its transformation products in surface water were calculated using the combined Pesticide Root Zone Model (PRZM) and Exposure Analysis Modeling System (EXAMS), which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in two types of vulnerable drinking water sources, a small reservoir (57-year simulation) and a prairie dugout (81-year simulation).

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing as well as geographic scenario. The Level 1 EEC estimate is expected to allow for future use expansion into other crops at this application rate. Appendix III, Table 9 lists the application information and main environmental fate characteristics used in the models.

EECs for the transformation products M2 and M3 were also estimated. The parent compound pinoxaden transforms rapidly to M2, which is considered to be the active form. Another transformation product, M3, is produced from both pinoxaden and M2.

The models were run first to simulate fate and transport of the parent pinoxaden. Then separate model runs were conducted for the two transformation products M2 and M3, assuming an application of an equivalent amount of parent compound. The application rate used in each transformation product simulation was equal to the parent application rate adjusted by the molar ratio of the transformation product to the parent compound, conservatively assuming 100 percent transformation of parent to the transformation product. Appendix III, Table 10 provides the EECs calculated in the Level 1 drinking water assessment.

5.9.3 Vegetation and Other Food Sources

Maximum EECs for pinoxaden and for the end-use product AXIAL 100EC Herbicide in vegetation and insects were determined using a nomogram developed by the USEPA from the data of Hoerger and Kenaga (1972) and Kenaga (1973), and modified according to Fletcher et al. (1994) using a total application of 0.06 kg a.i./ha and 0.618 kg EP/ha per season (one application) (Appendix II, Tables 11-16).

6.0 Effects on Non-target Species

6.1 Effects on Terrestrial Organisms

Pinoxaden
Pinoxaden is expected to be of low toxicity to terrestrial animals; however, the acute oral toxicity to bees in currently unknown. No significant adverse effects were seen in terrestrial annelids. The LC_{50} for pinoxaden to earthworms was >1000 mg/kg soil and the NOEC value was 178 mg/kg soil. Pinoxaden is practically non-toxic to honeybees on an contact toxicity basis (NOEL = 6.3 µg a.i./bee, LD_{50} >100 µg a.i./bee).The acute oral study was found to be unacceptable and is currently a data gap. Based on the lack of toxicity in the honeybee contact toxicity study, the waiver submitted for predators and parasites was found to be acceptable as the predator and parasite studies are on an acute contact basis.

Pinoxaden is practically non-toxic to upland game birds and waterfowl on both an acute oral and dietary exposure basis. The acute NOEL and LD_{50} for oral dosing was 810 and >2250 mg a.i./kg bw, respectively, for northern bobwhite quail. The acute NOEC and LC_{50} for dietary exposure of the northern bobwhite quail were 5970 and >5970 mg a.i./kg dw diet, respectively, and for dietary exposure the mallard duck were 3220 and >5970 mg a.i./kg dw diet, respectively. The avian reproductive toxicity of pinoxaden has not been studied.

Pinoxaden is expected to have a low acute toxicity to small wild mammals such as rats (LD_{50} >5000 mg/kg bw). No adverse effects were observed from dietary exposure of pinoxaden to rats and mice for thirteen weeks (NOAEL of 5000 and 2500 (males only) mg a.i./kg diet, respectively).

M2
The transformation product M2 is expected to be of low toxicity to terrestrial animals. No significant adverse effects were seen in terrestrial annelids. The LC_{50} for M2 to earthworms was >1000 mg/kg soil and the NOEC was 556 mg/kg soil. There is no information regarding the toxicity of M2 to honeybees via oral or contact routes of exposure. In the avian reproduction

study, only M2 was tested, not the parent compound pinoxaden. For the northern bobwhite quail, there was significant reduction in the number of viable embryos compared to controls as a percentage of eggs set (86% and 82% versus 96%) at the two highest concentrations. No treatment-related effects on reproductive performance were seen at any of the concentrations tested in the mallard duck study. The NOEC for M2 to the bobwhite quail and mallard duck based on the reproductive parameters were 107 and 1050 mg a.i./kg dw, respectively. The toxicity of M2 to mammals and birds is expected to be addressed through the pinoxaden toxicity studies. Pinoxaden metabolises to M2 in rats in less than one hour.

M3

The transformation product M3 may be toxic to terrestrial animals. No significant adverse effects were seen in terrestrial annelids. The LC_{50} for M3 to earthworms was >1000 mg/kg soil and the NOEC value was 178 mg/kg soil. There is no information regarding the toxicity of M3 to honeybees via oral or contact routes of exposure. The M3 was slightly acutely toxic to rats (LD_{50} = 1098 mg/kg bw). Rats exhibited clinical signs of toxicity, including diarrhea, piloerection, upward curvature of the spine, irregular breathing, reduced activity, reduced stability, tip toe gait and sides pinched.

AXIAL 100EC Herbicide

The toxicity of the end-use product AXIAL 100EC Herbicide to earthworms was not assessed. The toxicity of AXIAL 100EC Herbicide to honeybees is classified as practically non-toxic on an acute contact (LC_{50} of 84.0 µg EP/bee) and acute oral basis (LD_{50} of 9.3 µg EP/bee). AXIAL 100EC Herbicide is expected to have low toxicity to mammals (LD_{50} >5000 mg/kg bw). Exposure to AXIAL 100EC Herbicide resulted in significant reduction in seedling emergence for ryegrass with an EC_{25} of 207.9 g EP/ha and an estimated EC_{25} of 1480.2 g EP/ha in lettuce. In the vegetative vigour study, there was significant reductions in biomass in both the oat and the cabbage with EC_{25} values of 53.8 and 990.1 g EP/ha, respectively.

ADIGOR Adjuvant

ADIGOR Adjuvant (A12127S formulation) is expected to be of low toxicity to terrestrial organisms. It is practically non-toxic to bees on both an acute oral (LC_{50} >200 µg/bee) and acute contact (LD_{50} >200 µg/bee) toxicity basis. Exposure of ADIGOR Adjuvant (A12127S formulation) as a control when testing AXIAL 100EC Herbicide (concurrent submission 2004-0698) resulted in significant reductions in *Lolium perenne* seedling emergence; however, the effect was less than 25%.

6.2 Effects on Aquatic Organisms

Precipitation of pinoxaden and M2 was found in the aquatic toxicity studies submitted (at 0.04 and 0.03% of the reported solubilities), and analytical samples were acidified prior to analysis. This is not acceptable because exposure concentrations cannot be determined upon acidification and, thus, endpoints cannot be calculated. A complete aquatic data set may have indicated greater toxicity. The toxicity of pinoxaden to freshwater invertebrates, cold water fish species and freshwater vascular plants is unknown. In warm water fish species, pinoxaden was found to have toxic effects (sublethal). There were no chronic studies conducted with pinoxaden to determine if there are any reproductive effects. Based on the PMRA review of green algae, pinoxaden has toxic effects to freshwater algae, causing reductions in algal growth. There are further studies currently under review.

In the marine environment, pinoxaden is highly toxic to sessile invertebrates (IC_{50} 0.32 mg a.i./L; calculated NOEC of 0.032 mg a.i./L). The toxicity to pelagic invertebrates and marine fish are unknown as the submitted studies were deemed unacceptable. Pinoxaden is toxic to marine algae. There were issues with pinoxaden stability in this study. However, both the biomass IC_{50} (1.0 mg a.i./L) and NOEC (0.62 mg a.i./L) were within the valid range of the test concentrations; therefore, this study is acceptable.

The toxicity of the transformation products, M2 and M3, has not been completely reviewed at this time.

A12127R is moderately toxic to freshwater invertebrates and fish. A12127R is toxic to freshwater algae, causing reductions in algal growth. No marine studies are required at this time.

6.3 Effects on Biological Methods of Sewage Treatment

This data is currently not required by the PMRA.

6.4 Risk Characterization

The risk assessment integrates the exposure and ecotoxicology data to estimate the potential for adverse ecological effects. The PMRA currently conducts a deterministic risk assessment of pest control products. Environmental risk is characterized using the risk quotient (RQ) method, which is the ratio of the EEC divided by the toxicity endpoint. Risks are then classified based on the scheme presented below:

Risk Classification Scheme

Risk Quotient (RQ)	Risk Category
< 0.1	Negligible risk
≥ 0.1 to < 1	Low risk
≥ 1 to < 10	Moderate risk
≥ 10 to < 100	High risk
≥ 100 to < 1000	Very high risk
≥ 1000	Extremely high risk

The toxicity of the end-use product, AXIAL 100EC Herbicide, has been found to be more toxic than the technical grade active ingredient, pinoxaden, in most organisms where studies with both were conducted.

Thus, where possible, this risk assessment has been conducted with the end-use product rather than the active ingredient. Further studies will be required to complete the risk assessment.

6.4.1 Environmental Behaviour

In the terrestrial environment, pinoxaden is relatively non-volatile under field conditions (i.e., from dry and from wet or moist surfaces), nor does it undergo photolysis on soils. Pinoxaden, however, is not expected to be persistent in the terrestrial environment as it is susceptible to hydrolysis and readily undergoes biotransformation in both aerobic and anaerobic soils. Pinoxaden and/or its transformation products will not bind to soils over time.

The predicted mobility of pinoxaden was low to moderate on the basis of laboratory adsorption/desorption studies. M2 and M3 have very high predicted mobility. This was supported by terrestrial field studies that indicated almost all of the parent compound was found within the first 15-cm soil depth, whereas M2 was detected in the 15- to 30-cm depth and M3 was detected in the 45- to 60-cm soil depth.

Although pinoxaden is not applied directly to surface waters, it may reach the aquatic environment as a result of off-target spray drift or from overland run-off during heavy rainfall events. Based on laboratory and field trials, pinoxaden has a limited potential for leaching to groundwater and subsequent recharge to surface waters. However, M2 and M3 have a potential for leaching to groundwater and subsequent recharge to surface waters based on modeling results. Aerobic and anaerobic water–sediment laboratory studies indicate that once pinoxaden enters the aquatic environment, it will rapidly transform to M2 in the water column. It does not partition to sediment. Pinoxaden is non-persistent in aerobic and anaerobic aquatic environments with DT_{50}s of no more than 0.3 days. M2 is, at most, only slightly persistent in aerobic and anaerobic aquatic environments with DT_{50}s of up to 20.6 days. M3, however, is expected to be persistent under aerobic and anaerobic aquatic conditions. For modeling purposes, M3 was considered stable under aerobic conditions and a half-life of 96 days was estimated from the data under anaerobic conditions.

For pinoxaden and M2, the major routes of transformation are aerobic and anaerobic biotransformation. There are limited data with regards to M3; however, it is expected to undergo hydrolysis at higher pHs (half-lives of 57 days at pH 7; 0.9 days at pH 9).

In the terrestrial environment, ADIGOR Adjuvant (A12127S formulation) is expected to volatilise under field conditions (i.e., from dry and from wet or moist surfaces). It is not expected to be persistent in the terrestrial environment as it is susceptible to hydrolysis and biotransformation. None of the compounds within the ADIGOR Adjuvant (A12127S formulation) mixture are expected to be very mobile in soil, especially in light of their volatility and transformation rates.

Although ADIGOR Adjuvant (A12127S formulation) is not directly applied to surface waters, it may reach the aquatic environment as a result of off-target spray drift or from overland run-off during heavy rainfall events. Based on the literature, ADIGOR Adjuvant (A12127S formulation) has a limited potential for leaching to groundwater and subsequent recharge to surface waters. Once this adjuvant does enter the aquatic system, it is expected to hydrolyse and to biotransform fairly rapidly.

6.4.2 Terrestrial Organisms

6.4.2.1 Earthworms

The estimated initial EEC for pinoxaden based on the maximum allowable application is 0.027 mg a.i./kg soil. Based on the observed NOEC of 178 mg a.i./kg, the pinoxaden and M3 RQs for earthworms are 1.5×10^{-4}, and the M2 RQ for earthworms is 4.9×10^{-5}. The risk of lethal and sublethal effects of pinoxaden and its transformation products to earthworms is negligible (Appendix III, Table 17) with the application of pinoxaden to wheat and barley using groundboom equipment at a maximum allowable annual rate of 60 g a.i./ha.

6.4.2.2 Honeybees

Pinoxaden

Products that are applied as sprays can be evaluated initially by considering the likely exposure of bees and the toxicity of the product. Using Atkins et al. (1981), the pinoxaden acute contact NOEC endpoint (6.3 µg a.i./bee) is multiplied by 1.12 to convert to 7.1 kg a.i./ha. The EEC is the application rate of 0.06 kg a.i./ha, resulting in an RQ of 0.008. The risk of lethal and sublethal effects of pinoxaden to bees on an acute contact basis is negligible (Appendix III, Table 19) with the application of pinoxaden to wheat and barley using groundboom equipment at a maximum allowable annual rate of 60 g a.i./ha is negligible.

Pinoxaden is a systemic pesticide; therefore, it may be found in nectar after it has been applied. Thus, there is a potential risk to honeybees and other pollinators. However, the risk to honeybees through oral exposure causing 50% mortality could not be assessed for pinoxaden due to lack of acceptable data.

M2 and M3

There was no data provided for either transformation product; therefore, the risk could not be determined.

AXIAL 100EC Herbicide

Using Atkins et al. (1981), the acute contact and acute oral NOEC endpoints of AXIAL 100EC Herbicide (8.4 and 9.3 µg EP/bee, respectively) are multiplied by 1.12 to convert to 9.4 and 10.4 kg EP/ha, respectively. The EEC is the application rate of 0.618 kg EP/ha, resulting in RQs of 0.07 and 0.06. The risk of lethal and sublethal effects of AXIAL 100EC Herbicide to bees on an acute contact and an acute oral basis is negligible (Appendix III, Table 19) with the application of

AXIAL 100EC Herbicide to wheat and barley using groundboom equipment at a maximum allowable annual rate of 618 g a.i./ha.

ADIGOR Adjuvant

Using the classification of Atkins et al. (1981), the acute contact and acute oral NOEC endpoints (<12.5 and <12.5 µg A12127R/bee, respectively) for the A12127R formulation (the test adjuvant is very similar to ADIGOR Adjuvant, A12127S formulation) are multiplied by 1.12 to convert to <14 and <14 kg A12127R/ha, respectively. The EEC is the application rate of 0.645 kg A12127R/ha, resulting in RQs of 0.09 and 0.09. The risk of lethal and sublethal effects of A12127R to bees on an acute contact basis is negligible (Appendix III, Table 19) with the application of ADIGOR Adjuvant (A12127S formulation) to wheat and barley using groundboom equipment at a maximum allowable annual rate of 645 g a.i./ha.

6.4.2.3 Birds

Pinoxaden

Wild upland game birds and waterfowl, as represented by northern bobwhite quail and mallard duck, respectively, could be exposed to pinoxaden and its transformation products as a result of consumption of treated vegetation, contaminated prey or spray drift. The northern bobwhite diet may consist of approximately 30% small insects, 15% forage crops and 55% grain and seeds. The EEC in the bobwhite diet after the application of pinoxaden, based on the maximum application rate (60 g a.i./ha) is 10.5 mg a.i./kg dw diet. The mallard diet consists of approximately 30% large insects and 70% grain and seeds. The EEC in the mallard diet is 2.05 mg a.i./kg dw diet.

In the acute oral toxicity study with pinoxaden, the mean body weight per individual (BWI) of the female bobwhite quail in the control treatment was 0.202 kg bw/ind., while the mean food consumption (FC) was 0.035 kg dw/ind./day. The potential daily intake of pinoxaden (DI = FC × EEC) was calculated as 0.37 mg a.i./ind./day. The reported LD_{50} and NOEL values were >2250 and 810 mg a.i./kg bw, respectively. When expressed on a per individual basis, the LD_{50i} (=LD_{50} × BWI) was >455 mg a.i./ind., and the $NOEL_i$ (= NOEL × BWI) was 163 mg a.i./ind. Based on the DI, the LD_{50i} and the $NOEL_i$, it would take a bobwhite quail at least 440 days of continuous consumption of a contaminated diet to attain the dose equivalent to that administered in the laboratory by gavage that had no observable effect on the laboratory population and >1230 days to reach a dose equivalent to the administered in the laboratory by gavage that killed 50% of the test population (Appendix III, Table 19). Therefore, pinoxaden is unlikely to pose a risk to bobwhite quail when applied at the proposed maximum application rate.

The NOECs for lethal and sublethal effects in bobwhite quails and mallard ducks from dietary exposure were 5970 and 3220 mg a.i./kg diet, respectively. For sublethal effects, the EECs were lower than the NOECs for both species. The resulting RQs for sublethal toxicity effects from pinoxaden in bobwhites and mallards were 0.002 and 0.002, respectively (Appendix III, Table 19). Pinoxaden, therefore, poses a negligible risk to bobwhite quail and mallard ducks when applied at the proposed maximum application rate on a dietary basis.

Reproductive toxicity studies were conducted with the transformation product M2. Pinoxaden is not acutely toxic to birds and metabolises rapidly (less than one hour) in birds to the transformation product M2. Additionally, pinoxaden is not expected to persist in feed after a single application. Therefore, a reproductive study conducted with pinoxaden will not be required at this time.

M2

The NOECs for reproductive effects in bobwhite quails and mallard ducks from dietary exposure were 107 and 1080 mg/kg dw, respectively. For reproductive effects, the EECs were lower than the NOECs for both species. The resulting RQs for the transformation product M2 in bobwhites and mallards were 0.1 and 0.002, respectively (Appendix III, Table 19). M2, therefore, poses a low risk to bobwhite quail and a negligible risk to mallard ducks assuming 100% transformation of the parent compound at the proposed maximum application rate.

6.4.2.4 Small Wild Mammals

Small wild mammals such as rats, mice and rabbits may be exposed to residues of pinoxaden and its transformation products as a result of consumption of sprayed vegetation and/or contaminated prey. The EECs for pinoxaden in the diet of rats and mice are 30.27 and 30.09 mg a.i./kg dw diet.

The following data on BWI and food consumption estimates developed by the USEPA (1988) were used to determine risk to small wild mammals—rat BWI of 0.35 kg and FC of 0.06 kg dw/ind./day; mouse BWI of 0.033 kg and FC of 0.006 kg dw/ind./day.

Pinoxaden

The risk to small wild mammals from acute exposure to pinoxaden is not expected. Acute exposure of rat to pinoxaden resulted in an LD_{50} of >5000 mg a.i./kg bw. Based on a daily intake (DI = FC × EEC) of 1.8 mg a.i./ind./day, and a LD_{50i} (LD_{50} × BWI) of >1750 mg a.i./ind., a rat would require >972 (LD_{50i} ÷ DI) of continuous feeding on contaminated food sources to reach a dose equivalent to the administered in the laboratory by gavage that killed 50% of the test population. As the NOEL was not available, one-tenth of the LD_{50} was used in the risk assessment of the acute toxicity. The calculated NOEL is, therefore, >500 mg a.i./kg bw, and the $NOEL_i$ (NOEL × BWI) is >175 mg a.i./ind. Therefore, the maximum number of days of intake of pinoxaden by a wild rat to attain a dose equivalent to the administered by gavage in the laboratory that had no observable effect on the laboratory population is also one-tenth of the number of days of intake to accumulate a dose equivalent to that administered by gavage that killed 50% of the laboratory population. Thus, the maximum number of days of intake to reach the laboratory dosage that had no observable effect is >96 days. Therefore, pinoxaden in not expected to pose a risk to small wild mammals on an acute basis.

The risk to small wild mammals from chronic dietary exposure to pinoxaden is expected to be negligible. Exposure of pinoxaden to mice (males only) in the diet for 13 weeks resulted in a NOEL of 2500 mg a.i./kg diet for both lethal and sublethal effects. The EEC of pinoxaden in the mouse diet (30.09 mg a.i./kg dw diet) is much lower, resulting in an RQ of 0.012. Therefore, pinoxaden is not expected to pose a risk to small wild mammals from exposure through their diet.

Offspring development in rats was the most sensitive mammalian endpoint observed (NOEL = 30 mg a.i./kg bw/day). Using an EEC of 30.27 mg a.i./kg diet, the RQ is 1.01, which indicates a moderate reproductive risk to rats.

Based on the studies with rats and mice, pinoxaden may pose a reproductive risk to mammals in the wild.

M3

The risk to small wild mammals from acute exposure to the transformation product M3 is expected to be negligible. Acute exposure of rat to pinoxaden resulted in an LD_{50} of 1098 mg a.i./kg bw. Based on a daily intake (DI = FC × EEC) of 1.8 mg a.i./ind./day (assuming 100% transformation from the parent compound) and a LD_{50i} (LD_{50} × BWI) of 384 mg a.i./ind., a rat would require 214 days of continuous feeding on contaminated food sources to reach a dose equivalent to the administered in the laboratory by gavage that killed 50% of the test population. As the NOEL was not available for this study, one-tenth of the LD_{50} was used in the risk assessment of the acute toxicity. The calculated NOEL is, therefore, 109.8 mg a.i./kg bw and the $NOEL_i$ (NOEL × BWI) is 38.4 mg a.i./ind. The maximum number of days of intake is 21 days. Therefore, M3 is not expected to pose a risk to small wild mammals on an acute basis.

The risk to small wild mammals from chronic dietary exposure to the transformation product M3 is expected to be negligible. Exposure of M3 to rats in the diet for 13 weeks resulted in a NOEL of 1000 mg a.i./kg diet for both lethal and sublethal effects. The EEC for M3 (assuming 100% transformation from the parent) in the rat diet is much lower, resulting in an RQ of 0.03. Therefore, M3 poses a negligible risk to small wild mammals from exposure through their diet.

AXIAL 100EC Herbicide

The EECs for AXIAL 100EC Herbicide in the diet of rats and mice are 311.78 and 309.90 mg a.i./kg dw diet.

The risk to small wild mammals from acute exposure to the EP AXIAL 100EC Herbicide is expected to be negligible. Acute exposure of rat to AXIAL 100EC Herbicide resulted in an LD_{50} of 3129 mg/kg bw and an NOEC of 312.9 mg/kg bw (based on $1/LD_{50}$). Based on a daily intake (DI = FC × EEC) of 18.7 mg/ind./day, a $LD50_i$ (= LD_{50} × BWI) and an $NOEC_i$ (= NOEC × BWI) of 1095 and 109.5 mg/ind., a rat would require 59 and 5.9 days of continuous feeding on contaminated food sources to reach a dose equivalent to the administered in the laboratory by gavage that killed 50% of the test population and the no-adverse effects dose, respectively. Therefore, AXIAL 100EC Herbicide is not expected to pose a risk to small wild mammals on an acute basis.

6.4.2.4 Terrestrial Plants

AXIAL 100EC Herbicide

The risk of AXIAL 100EC Herbicide to non-target terrestrial vascular plants was assessed for a single application of this product at rates ranging from 0.547 to 140 g a.i./ha (5.7 to 1480.2 g EP/ha) in both seedling emergence and vegetative vigour studies. For seedling emergence, the most sensitive monocot species was rye grass based on biomass, with an EC_{25} of 207.9 g EP/ha (NOEC 92.0 g EP/ha). The most sensitive dicot species was lettuce, which exhibited significant reduction in emergence, survival and biomass (24–27%) at the 1480.2 g EP/ha rate (NOEC 35 g a.i./ha). The RQs for seedling emergence based on the EEC for AXIAL 100EC Herbicide (618 g EP/ha), based on EC_{25} values, are 3.0 and 0.4 for ryegrass and lettuce, respectively. For vegetative vigour, the most sensitive monocot species was oats based on biomass, with an EC_{25} of 53.8 g EP/ha (NOEC 22.9 g EP/ha). The most sensitive dicot species was cabbage based on biomass, with an EC_{25} of 990.1 g EP/ha (NOEC 92.0 g EP/ha). The RQs for vegetative vigour, based on EC_{25} values, are 11.5 and 0.6 for oats and cabbage, respectively. Therefore, the risk of lethal and sublethal effects to terrestrial plants is moderate to high.

The overall risk to terrestrial organisms ranges from negligible to high. Pinoxaden does not pose a risk to terrestrial invertebrates and small wild mammals. Pinoxaden may pose a low risk to birds based on dietary toxicity. The transformation product M3 is expected to pose a negligible risk to small wild mammals. Pinoxaden will pose a high risk to non-target, terrestrial vascular plants.

ADIGOR Adjuvant

The risk of ADIGOR Adjuvant (A12127R formulation) to non-target terrestrial vascular plants was assessed for a single application of the adjuvant. The most sensitive species resulted in an NOEC of >4000 g A12127R/ha. The RQs for seedling emergence, based on the NOEC (only data point provided), is 0.2. The risk to terrestrial plants is low; however, RQs for terrestrial plants are normally calculated with EC_{25} values, not NOEC values. Therefore, this assessment is more conservative than required.

6.4.3 Aquatic Organisms

Due to a number of issues with the aquatic toxicological package provided in this submission, there is a limited data set from which to conduct an aquatic risk assessment. Therefore, the risk assessment is based on the toxicity of the end-use product and the technical grade active ingredient.

Although the proposed use does not include direct application to water, the possibility that aquatic organisms would be exposed to pinoxaden cannot be ruled out. As with the terrestrial organisms, the degree of risk to aquatic organisms is assessed by determining RQs, which compare a screening level scenario EEC (30 cm of surface water as a result of direct overspray) with acute toxicity (i.e., EEC ÷ NOEC).

The toxicity of pinoxaden to daphnids (acute and chronic), mysid (acute), rainbow trout (acute and chronic), sheepshead minnow (acute), and vascular plants is not known. Toxic effects were found for pinoxaden to fathead minnows (*Pimephales promelas*) and blue-green algae (*Anabaena flos-aquae*), green algae (*Selenastrum capricornutum*) and the EP to freshwater algae (*Pseudokirchneriella subcapitata*). The 96-hour LC_{50} for fathead minnows was 20 mg a.i./L and the resulting NOEC was 16 mg a.i./L. An RQ of 0.001 (Appendix III, Table 20) for fathead minnows indicates that there is negligible risk from pinoxaden at the proposed rates to warm water fish. Blue-green algae was found to be more sensitiva than green algae; therefore, RQs were only calculated for blue-green algae. Growth of freshwater blue-green algae was significantly inhibited by pinoxaden. The NOEC of 0.13 mg a.i./L resulted in an RQ of 0.2, or low risk to freshwater algae. Growth of freshwater green algae was significantly inhibited by AXIAL 100EC Herbicide. The NOEC of 0.043 mg EP/L resulted in an RQ of 4.8, or moderate risk to freshwater algae. It should be noted that no other studies have been reviewed/accepted with the parent compound in freshwater. Further review on requested studies may alter the risk assessment for freshwater algae.

Of the four marine studies submitted, only two were found acceptable; oyster shell deposition and marine diatom. The NOEC for oyster exposure was 0.032 mg a.i./L, which results in an RQ of 0.6 (Appendix III, Table 20). Therefore, pinoxaden represents a low risk to sessile marine organisms. The NOEC based on inhibition for marine diatoms was 0.62 mg a.i./L, resulting in an RQ of 0.03, or negligible risk.

The estimated EEC in water for ADIGOR Adjuvant (A12127S formulation) based on the maximum allowable application is 0.29 mg A12127S/L. Based on the observed NOEC for *daphnia* species of 0.31 mg/L, the RQ is 0.94. The risk of lethal and sublethal effects of ADIGOR Adjuvant (A12127S formulation) to daphnids is low to moderate risk. Based on the observed NOEC for rainbow trout of 2.2 mg/L, the RQ is 0.13. The risk of lethal and sublethal effects of ADIGOR Adjuvant (A12127S formulation) to fish is low.

6.5 Risk Mitigation

Based on the data submitted and on the existing data requirements for use-site categories 13 and 14, an assessment of the environmental safety associated with the use of pinoxaden has been conducted. Application of the technical grade active ingredient pinoxaden and the formulated end-use product AXIAL 100EC Herbicide using a scenario of a single application at the maximum rate of 60 g a.i./ha has identified areas of concern, particularly with terrestrial non-target plants and aquatic organisms (i.e., algae and invertebrates). The risk to freshwater aquatic organisms will be re-assessed in the future upon receiving the studies requested. Application of ADIGOR Adjuvant (A12127S formulation) using a scenario of a single application at the maximum rate of 700 mL/ha (645.7 g A12127S/ha) has identified a potential for concern with regards to aquatic invertebrates and algae.

Buffer Zones

Based on the proposed application rates, the following buffer zones to protect sensitive aquatic habitats are recommended to mitigate risks. Further mitigative label statements, as outlined in

Section 6.5, are required for the label of the manufacturing technical product and the end-use product. Based on the RQ of 4.8 for green algae, a buffer zone of under 20 m is expected. This value can not be specifically calculated at this time as all study data evaluation reports have not been received from the USEPA. If a more sensitive species is noted in the complete review, the buffer zone size may increase. As the buffer zones are based on the end-use product rather than the active ingredient, future submissions containing pinoxaden with different formulations may require bridging toxicity data.

7.0 Efficacy

7.1 Mode of Action

Pinoxaden is a WSSA Group 1 herbicide belonging to a new class of ACCase inhibitors, the PPZs. This new chemistry was developed in the mid 1990s, after the development of APP in 1975 and CHD in 1986.

Pinoxaden (NOA 407855—internal code) is a selective postemergent grass herbicide with uptake by the leaves. After foliar absorption, Pinoxaden is translocated to the meristematic tissue, where it is degraded to the pro-herbicide M2. Inhibition of the ACCase enzyme initially is demonstrated as discoloration of young meristematic tissue. Thorough coverage of the plants is essential for consistent control. Actively growing susceptible grasses stop growing within 48 hours of treatment. Depending on species, growing conditions and crop competition, leaves and growing points turn yellow within one to three weeks after application. Further color changes and loss of vigor will be observed, followed by a browning and control three to five weeks after application. A unique feature of pinoxaden is the measured activity on both the chloroplastic and cytosolic target sites of the ACCase enzyme of susceptible grassy weeds. This is in contrast to established APP and CHD herbicide chemistries, which are only active on the chloroplast ACCase location.

Pinoxaden is similar to established APP chemistry in that the herbicidal active ingredient must be formulated with a safener to confer safety to target crops while maintaining selective annual grass control. In this regard, pinoxaden must be combined with cloquintocet-mexyl (CGA 185072) to protect target crops from ACCase inhibition after herbicide application.

The safening activity of cloquintocet-mexyl enables target crops to metabolize the herbicide faster than susceptible grass weeds by inducing metabolic enzymes to degrade the compound into non-phytotoxic compounds before crop damage can occur.

7.2 Effectiveness Against Pests

To support the new end-use product AXIAL 100EC Herbicide, the applicant submitted data from 188 efficacy trials conducted in Manitoba (73 trials), Saskatchewan (55 trials) and Alberta (60 trials) in 2000 (11 trials), 2001 (9 trials), 2002 (34 trials) and 2003 (134 trials).

There are two rates of application for AXIAL 100EC Herbicide. Adequate data were provided to determine that AXIAL 100EC Herbicide applied at a rate of 40 g a.i./ha is the lowest effective rate necessary to control Persian darnel (*Lolium persicum*). AXIAL 100EC Herbicide applied at a rate of 60 g a.i./ha will control wild oats (*Avena fatua*), green foxtail (*Setaria viridis*), yellow foxtail (*Setaria glauca*), volunteer oats (*Avena sativa*), volunteer canary seed (*Phalaris canariensis*) and proso millet (*Panicum miliaceum* L.). However, the data provided indicated that a rate lower than 60 g a.i./ha of AXIAL 100EC Herbicide may provide acceptable control of wild oats, green foxtail, yellow foxtail, volunteer oats, volunteer canary seed and proso millet. Additional data are requested to establish the lowest effective rate for control of these weeds.

AXIAL 100EC Herbicide may be tank-mixed with one of the following broadleaf herbicides:

- Refine Extra at 15 g a.i./ha
- Refine Extra + MCPA ester at 15 + 350 g a.i./ha
- Express Pack at 7.5 + 396 g a.i./ha
- Frontline Herbicide Tank Mix at 5 + 420 g a.i./ha
- Buctril M at 560 g a.i./ha
- Thumper at 560 g a.i./ha
- Mextrol 400M at 560 g a.i./ha
- Okay 450M (renamed Mextrol 450) at 562 g a.i./ha
- MCPA ester at 420–550 g a.i./ha
- MCPA amine at 420–550 g a.i./ha
- 2,4-D ester at 560 g a.i./ha
- Estaprop at 1019 g a.i./ha
- Prestige Herbicide Tank Mix at 144 + 660 g a.i./ha
- Curtail M at 660 g a.i./ha
- Trophy at 108+560g a.i./ha

With the tank-mixes of Refine Extra + MCPA ester, Frontline Herbicide Tank Mix, Thumper, and Express Pack, the claim for green foxtail is reduced to suppression.

7.2.1 Rainfastness of AXIAL 100EC Herbicide + Merge or ADIGOR Adjuvant (A12127S formulation) at 0.7 L/ha

Rainfastness of AXIAL 100EC Herbicide was reported in two trials conducted in 2003. One trial was conducted in the field in Saskatoon, Saskatchewan, and the other trial was conducted in a growth chamber at the University of Saskatoon, Saskatchewan. Based on the efficacy results of these two trials, a rainfastness interval of one hour was concluded to be acceptable.

7.2.2 Adjuvant Efficacy

The applicant requested the use of an adjuvant (Merge or ADIGOR Adjuvant [A12127S formulation] at 0.7 L/ha) with AXIAL 100EC Herbicide. Small-plot field trials were conducted in 2003 to confirm that AXIAL 100EC Herbicide requires one of the proposed adjuvants to achieve an acceptable level of weed control. The trials were conducted using sublethal use rates (20 and 40 g a.i./ha) to exaggerate differences between treatments and isolate the treatment effect of AXIAL 100EC Herbicide alone versus AXIAL 100EC Herbicide and 0.7 L/ha of adjuvant. The addition of an adjuvant to the alone treatment of AXIAL 100EC Herbicide enhanced the weed control of wild oats and green foxtail at 20 and 40 g a.i./ha. The need of an adjuvant (Merge or ADIGOR Adjuvant [A12127S formulation] at 0.7 L/ha) for the new end-use product AXIAL 100EC Herbicide was successfully demonstrated.

7.3 Phytotoxicity to Target Plants (Including Different Varieties) or to Target Plant Products

To support the new end-use product AXIAL 100EC Herbicide, the applicant submitted data from 74 dedicated crop tolerance trials conducted in Manitoba (15 trials), Saskatchewan (27 trials) and Alberta (32 trials) in 2002 (10 trials) and 2003 (64 trials). All dedicated crop tolerance trials included qualitative (crop phytotoxicity) and quantitative (crop yield) evaluations. In addition, crop phytotoxicity was assessed in 186 efficacy trials in Manitoba (73 trials), Saskatchewan (53 trials) and Alberta (60 trials). Efficacy trials were conducted in 2000 (11 trials), 2001 (9 trials), 2002 (34 trials) and 2003 (132 trials).

Adequate data were provided to support the postemergence use of AXIAL 100EC Herbicide in spring wheat (*Triticum aestivum*), durum wheat (*Triticum turgidum*) and barley (*Hordeum vulgare*) when spring wheat, durum wheat and barley are between the 1- and 6-leaf stage, prior to the 4th tiller. AXIAL 100EC Herbicide may be safely tank-mixed with the broadleaf herbicides listed in 7.2.

7.4 Impact on Succeeding Crops, Adjacent Crops and on Treated Plants or Plant Products Used for Propagation

7.4.1 Impact on Succeeding Crops

In support of the claim that no crop rotation limitations for the year following application are required on the AXIAL 100EC Herbicide label, seven true recropping field trials were conducted during the 2003 field season. A cereal (barley), an oilseed (canola) and a pulse crop (lentil) were used as representative "indicator crops" typical in cereal rotations common to western Canada. Trials were conducted in Alberta (two trials), Saskatchewan (two trials) and Manitoba (three trials). The data provided in the Canadian recropping trials as well as results provided under DACO Part 8 (Environmental Chemistry) of the submission to register these products indicate that pinoxaden and its degradate products would not be expected to have an effect on crops planted the following year. Therefore, crop rotation limitations for the year following application are not required.

7.5 Economics

The economic importance of spring and durum wheat production to the western Canadian economy is estimated to be $3.89 billion (CAD) and $1.06 billion per year for spring and durum wheat, respectively, based on 10-year average values. The annual value of barley production in western Canada has been estimated as $ 1.58 billion based on 10 year average figures (Canadian Wheat Board 2002).

Syngenta Crop Protection Canada developed an abridged economic model to estimate the impact of annual grass weeds on the production and overall value of wheat and barley in western Canada. The model determined the economic cost of a given weed was a function of the percent crop yield reduction (Saskatchewan Agriculture and Food 2003), the area treated (ha) (Stratus Agri-Marketing 2003), the average yield (t/ha) (Canadian Wheat Board 2002) and the average payment (CAD\$/t) (Canadian Wheat Board 2002). The use of this model provided conservative estimates of the cost of annual grass weeds in wheat in barley.

Wild oats are regarded as the most serious grassy weed in the agricultural regions of western Canada. Dew and Keys (1976) reported wild oat densities in excess of 10 plants/m^2 can reduce wheat yield by more than 10%. The Saskatchewan *Guide to Crop Protection 2003: Weeds, Plant Diseases, Insects* (2003) estimated that as wild oat densities approached 30 plants/m^2, barley yield could be reduced by 5–10%. Syngenta estimated that the economic loss in wheat due to wild oats can range from \$157–627 million. Similarly, this model has shown that even moderate infestations of wild oat in barley can result in an annual economic loss of over \$280 million.

Green foxtail is most prevalent in the western prairie provinces of Canada, and is currently considered to be the most abundant weed species in Saskatchewan and Manitoba. It is classified as a noxious weed in Manitoba, Saskatchewan and British Columbia, and is listed as a "Nuisance weed: prevent spread" in Alberta (United States Department of Agriculture [USDA] Invaders Database 2003). The Saskatchewan *Guide to Crop Protection 2003: Weeds, Plant Diseases, Insects* (2003) estimated that green foxtail populations of 250–350 plants/m^2 as the minimum economic threshold levels resulting in yield losses of 11–16% in wheat and 7–10% in barley. Using the same economic model as that used for wild oat, the cost of green foxtail can range from \$66–305 million in wheat and \$10–48 million in barley.

Persian darnel is now well established in the Peace River district of Alberta, the interlake region of Manitoba, and southwestern Saskatchewan. As a result of its highly competitive nature, it is expected to continue to spread across other regions within Western Canada. Very light infestations of Persian darnel (10 plants/m^2) can result in wheat yield losses of 11% (Saskatchewan Agriculture and Food 1995). As populations increase, the competitiveness of Persian darnel decreases; for example, 300 plants/m^2 would result in wheat yield losses of 28%. These populations of Persian darnel translate into annual economic loss in wheat of \$11.3–28.8 million. Losses in barley at the same populations (10–300 plants/m^2) are estimated to cost \$2.7–6.8 million annually.

Although not as troublesome as wild oats, green foxtail and Persian darnel, barnyard grass and yellow foxtail still have an economic impact on wheat and barley production. Heavier infestations of yellow foxtail can result in losses of up to \$2.6 million in wheat and \$500 000 in barley. Losses due to barnyard grass can ranger from \$3.7–17.1 million in wheat and up to \$2.6 million in barley. Additional "incidental weeds" controlled by AXIAL 100EC Herbicide that have a far lesser impact on yield, but still affect production, include volunteer oats, volunteer canary seed and proso millet.

7.6 Sustainability

7.6.1 Survey of Alternatives

7.6.1.1 Non-chemical Control Practices

Cultural control typically involves techniques other than pesticides to minimize the impact of a target pest on a given crop. Cultural practices include the following:

- sowing rotational crops in non cereal years to minimize pest damage in the year of cereal growth;
- shallow working of summer fallow fields;
- increased seeding rates; and
- shallow seeding to establish quick germination and stand establishment.

7.6.1.2 Chemical Control Practices

Alternative active ingredients registered for grass control in wheat and barley include, but are not limited to, clodinafop, fenoxaprop, tralkoxydim and diclofop (WSSA Group 1); flucarbazone and imazamethabenz (WSSA Group 2); and difenzoquat (WSSA Group 22, discontinued after 2005). In addition, glyphosate (WSSA Group 9) is used as a preseeding burnoff and for postharvest weed control.

7.6.2 Contribution to Risk Reduction and Compatibility with Current Management Practices Including Integrated Pest Management

AXIAL 100EC Herbicide can be used as part of an integrated pest management (IPM) strategy in both wheat and barley for hard to control common weeds in western Canada. Consistent control of highly competitive, hard-to-control weeds such as wild oats and Persian darnel will serve to reduce both pest populations and 'susceptibility of host'. The combination of consistent crop safety and lack of persistence in the soil also supports AXIAL 100EC Herbicide as a product compatible with integrated pest management. Consistent performance on all five important grassy weeds in western Canada coupled with the tank-mix flexibility will provide wheat growers with a broad-spectrum approach to weed control.

7.6.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

One of the most unique features of pinoxaden is the measured activity on both the chloroplastic and cytosolic target sites of the ACCase enzyme of susceptible grassy weeds. Preliminary results indicate that this secondary activity against enzyme activity (I50) within the cytosolic site represents a unique feature for pinoxaden relative to established APP and CHD herbicide chemistry which is only active on the chloroplastic ACCase location. Additional work is underway to study this differential response of the two iso-enzymes in more detail. Implications in the area of cross-resistance will be carefully studied with the intention of understanding some unusual observations of a unique cross-resistance pattern between APP/CHD resistant weeds relative to pinoxaden. Also the agronomic importance of an inhibition of the cytosolic ACCase will be studied in more detail. Additional experiments are also in progress to elucidate structural differences at the molecular target site for these three classes of ACCase inhibitors, which distinguishes pinoxaden enzyme binding from the structural requirements of established APP and CHD chemistry.

To address the issue of development of herbicide resistance, the AXIAL 100EC Herbicide label will be amended to include the resistance-management statement as outlined in Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*, as follows:

> HERBICIDE RESISTANCE MANAGEMENT:
>
> For resistance management, AXIAL 100EC Herbicide is a Group 1 herbicide. Any weed population may contain or develop plants naturally resistant to AXIAL 100EC Herbicide and other Group 1 herbicides. The resistant biotypes may dominate the weed population if these herbicides are used repeatedly in the same field. Other resistance mechanisms that are not linked to site of action, but specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance-management strategies should be followed
>
> To delay herbicide resistance:
>
> 1. Where possible, rotate the use of AXIAL 100EC Herbicide or other Group 1 herbicides with different herbicide groups that control the same weeds in a field.
>
> 2. Use tank mixtures with herbicides from a different group when such use is permitted.
>
> 3. Herbicide use should be based on an IPM program that includes scouting, historical information related to herbicide use and crop rotation, and considers tillage (or other mechanical), cultural, biological and other chemical control practices.
>
> 4. Monitor treated weed populations for resistance development. Prevent movement of resistant weed seeds to other fields by cleaning harvesting and tillage equipment and planting clean seed.
>
> 5. Contact your local extension specialist or certified crop advisors for any additional pesticide resistance-management and/or integrated weed-management recommendations for specific crops and weed biotypes.
>
> For further information or to report suspected resistance, contact company representatives at 1-800-665-9250 or at www.syngenta.ca.

7.7 Conclusions

Supported Uses for AXIAL 100EC Herbicide + Merge or ADIGOR Adjuvant (A12127S Formulation) at 0.7L/ha

Crops:	Spring wheat, durum wheat, barley
Timing of Application:	Postemergent when crops and weeds are at the 1- to 6-leaf stage, prior to the 4th tiller
Weed Control Claims:	Wild oats, green foxtail, yellow foxtail, Persian darnel, volunteer canary seed, proso millet
Rate of Application:	– 40 g a.i./ha for control of Persian darnel – 60 g a.i./ha conditionally accepted for control of remaining weeds
Spray Volume:	50–100L/ha
Tank-mix Partners:	Refine Extra, Refine Extra+MCPA*, Express Pack*, Frontline HTM*, Buctril M, Thumper*, Mextrol 400M, Mextrol 450, MCPA ester, MCPA amine, 2,4-D ester, Estaprop, Prestige HTM, Curtail M, Trophy
Rotational crops:	For fields treated with AXIAL 100EC Herbicide, no crop may be seeded until the following spring. There are no crop rotation limitations the year following application of AXIAL 100EC Herbicide.

* A claim of suppression only for green foxtail when tank-mixed with 60g a.i./ha of AXIAL 100EC Herbicide.

8.0 Toxic Substances Management Policy

During the review of pinoxaden and ADIGOR Adjuvant (A12127S formulation), the PMRA has taken into account the federal Toxic Substances Management Policy[1] (TSMP) and has followed its Regulatory Directive DIR99-03[2]. It has been determined that this product does not meet TSMP Track 1 criteria because of the following:

- Pinoxaden does not meet the criteria for persistence. Its values for half-life in air (not applicable), water (< 1 day), soil (0.2 to 5 day) and sediment (<1 day) are below the

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[1] The federal Toxic Substances Management Policy is available through Environment Canada's website at www.ec.gc.ca/toxics

[2] Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, is available through the Pest Management Information Service. Phone: 1-800-267-6315 within Canada or 613-736-3799 outside Canada (long distance charges apply); Fax: 613-736-3798; E-mail: pmra_infoserv@hc-sc.gc.ca; or through our website at www.pmra-arla.gc.ca

TSMP Track 1 cut-off criteria for air (≥2 days), water (≥182 days), soil (≥182 days) and sediment (≥365 days). ADIGOR Adjuvant (A12127S formulation) does not meet the criteria for persistence. Its values for half-life in air (unknown), water (unknown), soil (7 days) and sediment (unknown) are below the TSMP Track 1 cut-off criteria for air (≥2 days), water (≥182 days), soil (≥182 days) and sediment (≥365 days).

- Pinoxaden is not bioaccumulative. The pinoxaden log K_{ow} is 3.2 and pinoxaden is rapidly transformed to M2 through metabolic processes. The log K_{ow} for M2 is 0.6–1.7. Both are below the TSMP Track 1 cut-off criterion *n*-octanol–water partition coefficient (log K_{ow}) of ≥5.0. ADIGOR Adjuvant (A12127S formulation) is expected to be bioaccumulative. Studies have shown that the *n*-octanol–water partition coefficient (log K_{ow}) values range from 6.29–8.35, which are above the TSMP Track 1 cut-off criterion of ≥5.0. However, plant-based oils are expected to be metabolised.

- For toxicity, refer to Sections 3.6, 4.7 and 6.4.

- Pinoxaden does not form any major transformation products that meet the TSMP Track 1 criteria. ADIGOR Adjuvant (A12127S formulation) does not appear to form any major transformation products that meet the TSMP Track 1 criteria.

- Pinoxaden (technical grade) does not contain any by-products or microcontaminants that meet the TSMP Track 1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process. ADIGOR Adjuvant (A12127S formulation) does not contain any by-products or microcontaminants that meet the TSMP Track 1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

Pinoxaden nor its transformation products do not meet the criteria for TSMP Track 1 substances. The formulated product does not contain any formulants known to contain TSMP Track 1 substances. ADIGOR Adjuvant (A12127S formulation) does not meet the criteria for TSMP Track 1 substances.

9.0 Regulatory Decision

Pinoxaden, AXIAL Herbicide and ADIGOR Adjuvant (A12127S formulation) have been granted temporary registrations for the control of grass weeds in durum wheat, spring wheat and barley, pursuant to the Pest Control Products Regulations, subject to submission of the following:

- Statement of Product Specification Form (SPSF)
- Batch data
- Water solubility
- Enforcement Analytical Methodology—Livestock Matrices
- Freezer Storage Stability—Processed Commodities
- Analytical method in water (pinoxaden and NOA 407854)

- Acute oral bee toxicity study (pinoxaden)
- Acute toxicity to *Daphnia* sp. (pinoxaden and AXIAL 100EC Herbicide)
- Acute toxicity to coldwater fish (pinoxaden and AXIAL 100EC Herbicide)
- Toxicity to freshwater algae (NOA 407854)
- Toxicity to freshwater algae (NOA 447204)
- Toxicity to freshwater vascular plant (pinoxaden and AXIAL 100EC Herbicide)
- Toxicity to freshwater vascular plant (NOA 407854)
- Toxicity to freshwater vascular plant (NOA 447204)
- Efficacy

List of Abbreviations

°C	degree(s) Celsius
µg	microgram(s)
a.i.	active ingredient
ACCase	acetyl CoA carbolylase
AAP	aryloxyphenoxypropianates
ACN	acetonitrile
AD	administered dose
BBCH	BASF, Bayer, Ciba-Geigy and Hoechst
BWI	body weight per individual
CAS	Chemical Abstracts Service
CHD	cyclohexodione
CI	confidence interval
C_{max}	maximum concentration
DAT	day(s) after treatment
DCM	dichloromethane
DI	dietary intake
dpm	disintegrations per minute
DT_{50}	dissipation time 50%
EC	emulsifiable concentrate
EC_{25}	effect concentration 25%
EC_{50}	effect concentration 50%
ECD	electron capture detector
EE	ethyl ether
EEC	expected environmental concentration
EP	end-use product
ESI	electrospray ionization
EXAMS	Exposure Analysis Modeling System
FC	food consumption
FID	flame ionization detection
GC	gas chromatography
GD	gestation day
GLC	gas liquid chromatography
IC_{50}	inhibition concentration 50%
ILV	independent laboratory validation
IUPAC	International Union of Pure and Applied Chemistry
HAFT	highest average field trial
HCl	hydrochloric acid
HDPE	high-density polyethelene
HPLC	high performance liquid chromatography
$K_{d\text{-}ads}$	adsorption coefficient
$K_{d\text{-}des}$	desportion coefficient
K_{oc}	adsorption quotient normalized to organic carbon
$K_{oc\text{-}ads}$	organic carbon adsorption coefficient
$K_{oc\text{-}des}$	organic carbon desporption coefficient

K_{ow}	*n*-octanol–water partition coefficient
L	liter(s)
LC	liquid chromatography
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LD_{50i}	lethal dose 50% per individual
LEACHM	Leaching Estimation and Chemistry Model
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
MAS	maximum average score
MIS	maximum irritation score
MMAD	mass median aerodynamic diameter
MOE	margin of exposure
MRL	maximum residue limit
MS/MS	tandem mass spectrometry
ng	nanogram(s)
NOAEL	no observed adverse effect level
NOEL	no observed effect level
$NOEL_i$	no observed effect level (individual)
NOEC	no observed effect concentration
NPD	nitrogen phosphorus detector
Pa	Pascal(s)
PBI	plantback interval
PE	petroleum ether
pg	picogram(s)
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
ppb	parts per billion
PPZ	phenylpyrazolin
PRZM	Pesticide Root Zone Model
r^2	coefficient of determination
ROC	residue of concern
RQ	risk quotient
rrtc	relative retention time to chlorpyrifos
RSD	relative standard deviation
SD	standard deviation
SPE	solid phase extraction
TLC	thin-layer chromatography
TRR	total radioactive residue
USDA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WSSA	Weed Science Society of America

Appendix I Toxicology

Table 1 Toxicology Summary

METABOLISM—Rat			
Rate and extent of absorption and excretion: Rapidly absorbed. The low dose had a blood C_{max} within 1 hour. The initial half-life was approximately 1 hour in males and females. Terminal half-life was 6 hours. For the high dose, the blood C_{max} was between 1 and 12 hours. The elimination half-life was between 1 and 12 hours for both sexes. In repeat dose studies, the radioactivity level was below LOQ within 50 hours. Excretion was rapid with approximately 90% within 72 hours—urine: 59–78%, feces: 25–28% (biliary accounted for about 2/3 of dose). Tissues and carcass had less than 2% after 7 days. Both single and repeat dose had similar excretion profiles. **Distribution/target organ(s):** After 7 days, following single oral dose, only liver, kidney, blood and plasma were above LOQ. For repeat dose, all tissues had values higher than the LOQ; however, these values were always lower than the blood value (<0.003 ppm equivalent) with the same tissues as seen in the single oral dose having higher concentrations than other tissues. **Metabolism:** Similar regardless of level, sex or duration of dosing. The major metabolites are M2 (63–91% dose in excreta) and M4 (5–13% dose in excreta). Thirty-three other metabolites were identified in 7 fractions; however, each fraction was less than 3.3% and included 2–7 metabolites. No parent was detected in the excreta. Probable metabolism involves the initial hydrolysis of the ester moiety to form M2. To minor extent, M2 is also metabolized to form wide variety of minor metabolites including hydroxylation to form M4. **Other Species:** Also tested in mouse and rabbit. Essentially, the metabolism was the same in the rabbit and mouse as in the rat.			
STUDY	**SPECIES, STRAIN AND DOSES**	**NOAEL and LOAEL mg/kg bw/day**	**TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS**
ACUTE STUDIES—TECHNICAL PRODUCT			
Oral	5/sex/dose Wistar rats **Dose Level:** 5000 mg/kg bw (limit dose)	LD_{50} > 5000 mg/kg bw	– One ♂ death with reddish small intestine, large intestine and cecum seen at necropsy – Soft feces – Hunched posture **Low Toxicity**
Dermal	5/sex/dose Wistar rats **Dose Level:** 2000 mg/kg bw (limit dose)	LD_{50} > 2000 mg/kg bw	– Slight weight loss in 3 ♀s during 1st week then weight gain for rest of study **Low Toxicity**

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Inhalation	5/sex/dose Wistar rats **Dose Levels:** 2.249, 3.793 and 5.454 mg/L (actual)	LC_{50} = 4.63 mg/L	**≥2.249 mg/L** – Laboured breathing – Rales – Salivation – Ruffled fur – Hunched posture – Red secretion from nose – Symptoms of toxicity persisted 7 days **3.793 mg/L** – 3 animals found dead day 2 after exposure – Tachypnea, decreased activity **5.454 mg/L** – 4 animals found dead 1 day after exposure – 1 animal found dead day 3 after exposure – Bradypnea – Decreased activity – Red discolouration of lungs and red foci in the thymus of decedents at necropsy **Low toxicity**
Eye Irritation	3 (1 male and 2 female) New Zealand white rabbits **Dose Level:** 0.1 g	MIS = 13/110 at 1h MAS (24, 48, 72 h) = 12.6/110	– Corneal opacity persisting up to and including 24 days – Reddening of the conjunctiva up to 21 days – Chemosis up to 7 days – Reddening of the sclera up to 28 days – Conjunctival discharge up to 17 days **Severely Irritating** **(DANGER – CORROSIVE TO EYES)**
Skin Irritation	3 (1 male and 2 female) New Zealand white rabbits **Dose Level:** 0.5 g	MIS = 0/8.0 at 1 h MAS(24, 48, 72 h) = 0/8.0	– None
Skin Sensitization (Buehler)	30 guinea pigs (5/sex for control and 10/sex for test) **Dose Levels:** 1st Induction – 5% 2nd Induction – 50% Challenge – 50%	Negative	– None
ACUTE STUDIES—METABOLITES			
Oral (Up and Down Method) on **SYN 519312**	5 female Alpk:AP$_f$SD rats **Dose Levels:** 175, 550 and 2000 mg/kg bw (limit dose)	LD_{50} > 2000 mg/kg bw	– Piloerection, pinched sides and upward curvature of the spine on day 1 for the 1 animal dose at 175 mg/kg bw **Low Toxicity**

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Oral (Up and Down Method) on **NOA 447204 (M3)**	7 female Alpk:AP$_f$SD rats **Dose Levels:** 175, 550 and 2000 mg/kg bw (limit dose)	LD$_{50}$ = 1098 mg/kg bw (95% CI—550–2000 mg/kg bw)	**175 mg/kg bw** – Diarrhea, piloerection and upward curvature of the spine—recovery by day 2 **550 mg/kg** – Curvature of the spine, reduced splay reflex, irregular breathing, reduced activity, reduced stability, tip toe gait and sides pinched—recovery by day 2 **2000 mg/kg bw** – All killed *in extremis* on day 1 with curvature of the spine, reduced splay reflex, irregular breathing, reduced activity, reduced stability, tip toe gait and sides pinched and necropsy findings of red spots on the thymus (1/3) and unilateral pelvic dilation of the kidney (1/3) **Slight Toxicity** **(CAUTION – POISON)**
Oral (Up and Down Method) on **SYN 502836 (M6)**	5 female Alpk:AP$_f$SD rats **Dose Levels:** 175, 550 and 2000 mg/kg bw (limit dose)	LD$_{50}$ >2000 mg/kg bw	– None **Low Toxicity**
Oral (Up and Down Method) on **SYN 505887 (M10)**	4 female Alpk:AP$_f$SD rats **Dose Levels:** 550 and 2000 mg/kg bw (limit dose)	LD$_{50}$ >2000 mg/kg bw	– Slight upward curvature of the spine in 1 550 mg/kg bw animal **Low toxicity**
ACUTE STUDIES—FORMULATION (AXIAL 100EC Herbicide)			
Oral (Up and Down Method)	9 female Sprague Dawley rats **Dose Levels:** 175, 550, 1750 and 5000 mg/kg bw (limit dose)	LD$_{50}$ = 3129	**1750 mg/kg bw** – Hunched posture – Clear ocular discharge – Hypoactivity – Reduced fecal volume – All symptoms cleared by day 2 **5000 mg/kg bw** – 4/4 deaths – Hypoactivity – Abnormal posture – Piloerection – Anogenital staining **Low toxicity**

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Dermal	5/sex/dose Alpk:AP$_f$SD rats **Dose Level:** 2000 mg/kg bw (limit dose)	$LD_{50} > 2000$ mg/kg bw	– Marked skin irritation with slight to extreme desquamation – Slight to moderate erythema and oedema – Slight to moderate scabbing – Increased sensitivity to touch – Symptoms resolved within 14 days **Low Toxicity**
Inhalation	5/sex/dose Alpk:AP$_f$SD rats **Dose Level:** 5.0 mg/L (limit dose)	$LC_{50} > 5.0$ mg/L	– Mild respiratory tract irritation – Mild/moderate toxicity – Full recovery by end of day 15 **Low Toxicity**
Skin Irritation	3 (1 male and 2 female) New Zealand white rabbits **Dose Level:** 0.5 mL	MIS = 4.0/8.0 at 48 and 72 hours MAS (24, 48, 72 h) = 3.9/8.0	– Well defined erythema up to day 14 – Slight oedema up to day 7 – Desquamation persisting up to day 14 **Moderately Irritating** **(WARNING – SKIN IRRITANT)**
Eye Irritation	3 (1 male and 2 female) New Zealand white rabbits **Dose Level:** 0.1 mL	MIS = 40/110 at 48 hours MAS (24, 48, 72 h) = 37.6/110	– Slight/mild corneal opacity (whole cornea) for 4 days – Slight iritis up to 4 days – Slight to moderate redness of the conjunctiva up to 17 days – Chemosis up to 10 days – Discharge up to 4 days—lachrymation, harderian or mucoid discharge, erythema, oedema, thickening and convolution of the eyelids, hemorrhage of the nictitating membrane and dried secretion around the periorbital skin lasting up to 21 days **Moderately Irritating** **(WARNING – EYE IRRITANT)**
Skin Sensitization (Buehler)	30 female guinea pigs (10 for control and 20 for test) **Dose Levels:** 9 Inductions – 50% Challenge – 10%	Negative	– None
ACUTE STUDIES—ADJUVANT (ADIGOR Adjuvant, A12127S formulation)			
Oral (Up and Down Method)	7 female Sprague-Dawley rats **Dose Levels:** 175, 550, 1750, 5000 mg/kg bw (limit dose)	$LD_{50} > 5000$ mg/kg bw	– Hunched back – Hypoactivity – Piloerection – Anogenital staining – Diarrhea – Reduced fecal volume **Low Toxicity**

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Dermal	5/sex Alpk:AP$_f$SD rats **Dose Level:** 5000 mg/kg bw (limit dose)	LD$_{50}$ > 5000 mg/kg bw	– Slight/moderate skin irritation – Slight desquamation **Low Toxicity**
Inhalation	5/sex Alpk:AP$_f$SD rats **Dose Level:** 2.5 mg/L (actual dose)	LC$_{50}$ > 2.5 mg/L	– Mild respiratory tract irritation – Laboured breathing – ↑ salivation – Dark material around facial area – Mild to moderate toxicity **Low Toxicity**
Eye Irritation	3 female New Zealand white rabbits **Dose Level:** 0.1mL	MIS = 6/110 at 1h MAS (24, 48, 72 h) = 0.88/110	– Conjunctival redness up to 3 days **Minimally Irritating**
Skin Irritation	3 male New Zealand white rabbits **Dose Level:** 0.5 g	MIS = 2.3/8.0 at 1h MAS (24, 48, 72 h) = 1.2/8.0	– Slight oedema lasting up to 4 days. **Mildly Irritating** **(CAUTION – SKIN IRRITANT)**
Skin Sensitization (Buehler)	30 female guinea pigs (10 for control and 20 for test) **Dose Levels:** 9 Inductions – 100% Challenge – 25%	Positive	**Potential Sensitizer** **(POTENTIAL SKIN SENSITIZER)**
SHORT-TERM TOXICITY			
28-day Dermal	10/sex/dose HanBrl:WIST rats **Dose Levels:** 0, 10, 100 and 1000 mg/kg bw (limit dose)	**NOAEL** = 1000 mg/kg bw **LOAEL** = not observed	– No treatment-related effects
28-day Inhalation	Waiver request: Waiver acceptable based on low volatility, the MMAD greater than 15 µm and low acute toxicity of pinoxaden.		
14-day Dietary Range-finding, non-guideline	2/sex/dose Alderly Park rats **Dose Levels:** 0, 1250, 2500, 5000 and 10 000 ppm		**10 000 ppm** – Body-weight loss days 2 and 3 (♂,♀) – ↓ body-weight gain (♂) – ↓ food consumption (♂)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
21-day Dietary Supplemental palatability, non-guideline	3/sex/dose CD-1 mice **Dose Levels:** 0, 1000, 3000 and 4000 ppm		**1000 ppm** – body-weight loss first 2–5 days (♂,♀) **3000 ppm** – Body-weight loss first 2-5 days and then body-weight gain (♂,♀) **4000 ppm** – ↓ food consumption (♂,♀) – ↑ waste food observed (♂,♀) – Body-weight loss (♂,♀)
28-day Gavage Range-finding, non-guideline	8/sex/dose Alpk:APfSD rats **Dose Levels:** 0, 300, 450, 600 and 1000 mg/kg bw/day (limit dose)		**≥600 mg/kg bw/day** – ↑ water consumption (♂) – Ketonuria and cortical tubular nephropathy (♂,♀) – ↑ plasma urea (♂) **1000 mg/kg bw/day** – ↓ body weight, body-weight gain (♂) – ↓ water consumption (♀) – ↑ relative (to body) kidney weight (♂)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
28-day Gavage Range-finding, non-guideline	8/sex/dose Alpk:AP$_f$SD rats **Dose Levels:** 0, 300, 600 and 1000 mg/kg bw/day (limit dose)		**≥600 mg/kg bw/day** – ↑ water consumption (♂,♀) – ↑ urinary volume (♂,♀) – Ketonuria (♂) – ↑ serum urea and creatinine (♂) – ↑ absolute and relative (to brain and to body) kidney weight (♂) – Minimal to marked renal tubular atrophy (♂) – Minimal to marked renal tubular casts (♂) – Renal tubular dilation (♂,♀) – ↑ absolute and relative (to body and to brain) liver weight (♀) – ↑ glycogen deposition in the liver (♂) **1000 mg/kg bw/day** – ↓ body-weight gain (♂,♀) – ↓ food efficiency (♂) – 1 death day 11 (♂) – Ketonuria (♀) – ↑ absolute kidney weight (♀) – Granulated kidney surface (♂) – Polymorphonuclear infiltration in kidney (♀) – Single cell necrosis in kidney (♂) – ↑ total serum bilirubin and aspartate aminotransferase (♂) – ↑ lymphocytic infiltration of the liver (♀) – ↑ leucocytosis based on ↑ neutrophils, lymphocytes and large unstained cells (♂) – ↓ hematocrit (♀) – ↑ relative (to body) adrenal and testes weights (♂)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
28-day Dietary (capsule) Range-finding, non-guideline	1/sex/dose Beagle **Dose Levels:** 250, 500 and 1000 mg/kg bw/day (limit dose)		**250 mg/kg bw/day** – speculated ↓ food consumption (♂) – no control for comparison **≥500 mg/kg bw/day** – Body-weight loss of about 1.0 kg between days 15 and 29 (♂,♀) – ↓ food consumption (♂) – Salivation at dosing (♂) – Pale and thin appearance (♂) **1000 mg/kg bw/day** – ↓ food consumption from day 14 (♀) – Body-weight loss (♂: 0.1 kg between days 22 and 29; ♀: 0.3 kg between days 8 and 29) – Salivation at dosing (♀) – Pale and thin appearance (♀) – ↑ incidence of regurgitation and vomiting (♂,♀)
90-day Gavage	10/sex/dose HanIbm:WIST rats **Dose Levels:** 0, 3, 10, 30, 100 and 300 mg/kg bw/day	NOAEL = 300 mg/kg bw/day (♂), 100 mg/kg bw/day (♀) LOAEL 300 mg/kg /day (♀), not observed in ♂	**300 mg/kg bw/day** – ↑ water consumption and urinary volume (♀) – ↑ creatinine (♀) Terminal Body Weights: 401.5g/256.1g (♂,♀) Food Consumption: 5.83g/4.78g (♂,♀) study mean

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
90-day Dietary with a 28-day Interim Kill	12/sex/dose Alpk:AP$_{f}$SD rats (90days) 5/sex/dose Alpk:AP$_{f}$SD rats (28days) **Dose Levels:** 0, 150, 1000, 5000 and 10 000 ppm (0/0, 15/16, 98/110, 466/527, 900/965 mg/kg bw for ♂/♀)	**NOAEL** = 5000 ppm (466/527 mg/kg bw/day for ♂/♀) **LOAEL** = 10 000 ppm (900/962 mg/kg bw/day for ♂/♀)	**90 day** **10 000 ppm** – ↓ body weight, body-weight gain (♂,♀) – ↓ food consumption (♂) – ↑ water consumption first 7 weeks (♂) – ↑ urine volume (♀) – Renal lesions – cysts (♂,♀) – cortical tubular basophilia/dilation/atrophy (♂,♀) – ectasia pelvis (♂) – transitional cell hyperplasia (♂) **Interim Study** **10 000 ppm** – ↓ body weight, body-weight gain (♂,♀) – ↓ food consumption (♂) – Cortical tubular basophilia/dilation/ atrophy (♂,♀) – ↓ cholesterol (♂,♀) Terminal Body Weights: 514.5g/280.5g (♂,♀) Food Consumption: 6.81/6.81 (♂,♀)
90-day Gavage	10/sex/dose CD-1 mice **Dose Levels:** 0, 10, 100, 400, 700 and 1000 mg/kg bw/day (limit dose)	**NOAEL** = 700 mg/kg bw/day **LOAEL** = 1000 mg/kg bw/day	**1000 mg/kg bw/day** – ↓ body-weight gain (♂,♀) – ↑ piloerection (♂,♀) – ↑ incidence and severity of renal tubular basophilia (♂) Terminal Body Weights: 38.7g/29.15g (♂,♀) Food Consumption: 5.47g/3.99g (♂,♀)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
90-day Dietary	10/sex/dose CD-1 mice **Dose Levels:** 0, 1000, 2500, 5000 and 7000 ppm (0/0, 140.9/165.9, 365.0/436.7, 708.2/900.6 and 992.3/1311.7 mg/kg bw/day for ♂/♀) (limit dose)	**NOAEL** = not observed in females, 2500 ppm (365.0 mg/kg bw/day) for males **LOAEL** = 1000 ppm (165.9 mg/kg bw/day) for females, 5000 ppm (708.2 mg/kg bw/day) for males	**≥1000 ppm** – ↓ body weight, body-weight gain (♀) **≥2500 ppm** – ↑ plasma alkaline phosphatase (♀) **≥5000 ppm** – ↓ body weight, body-weight gain (♂) – ↓ food efficiency (♂,♀) – ↓ corpora lutea in ovaries (♀) **7000 ppm** – ↑ eosinophils (♂) – ↓ plasma glucose (♀) – ↑ severity of preputial gland tubular dilation/glandular reduction (♂) Terminal Body Weights: 29.7g/17.6g (♂,♀) Food Consumption: 3.31g/2.64g (♂,♀)
90-day (capsule)	4/sex/dose Beagle **Dose Levels:** 0, 25, 100, 250 and 500 mg/kg bw/day	**NOAEL** = 100 mg/kg bw/day **LOAEL** = 250 mg/kg bw/day	**≥250 mg/kg bw/day** – ↓ food consumption (♂,♀) – ↓ body-weight gain (♀,♀) – ↑ incidence of fluid feces, vomit, regurgitation (♂,♀) – Thin appearance (♂,♀) – Dehydration (♂,♀) – Cold to touch (♂,♀) – ↓ activity (♂,♀) – Pale (♂,♀) **500 mg/kg bw/day** – ↓ body weight (♀) – All ♀'s were euthanized for humane reasons (week 5) – ↓ body weight, body-weight gain and food consumption (♂) – 1 ♂ exhibited clinical signs of toxicity body-weight loss, ↓ food consumption and was sacrificed (week 13) Terminal Body Weights: 11.87 kg/10.0 kg (♂,♀) Food Consumption: 237g/274g (♂,♀)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
12-month Capsule	4/sex/dose Beagle **Dose Levels:** 0, 5, 25, 125 mg/kg bw/day	**NOAEL =** 125 mg/kg bw/day **LOAEL** = not observed	No adverse effects.
SHORT-TERM TOXICITY for METABOLITES of PINOXADEN			
14-day Dietary (palatability, non-guideline) **NOA 447204 (M3)**	2/sex/dose Alderley Park rats **Dose Levels:** 0, 1250, 2500, 5000 and 10 000 ppm		**≥1250 ppm** – ↓ food consumption days 1–10 (♀) – ↓ body weight gain (♂,♀)
28-day Dietary (range-finding, non-guideline) **NOA 447204 (M3)**	5/sex/dose Alpk:AP$_f$SD rats **Dose Levels:** 0, 500, 3000, 6000 and 12 000 ppm (0/0, 64.9/66.9, 388.4/383.4, 805.6/769.7 and 1404.5/1423.3 mg/kg bw/day for ♂/♀) (limit dose)		**≥3000ppm** – ↓ food consumption (♂, ♀) – ↓ water consumption (♂) – ↑ absolute and relative (to terminal body weight) liver weight (♀) – ↑ incidence in minimal to slight non-zonal increased eosinophilia/reduced glycogen in the liver (♂) **12 000 ppm** – ↓ leucocytes, neutrophils, eosinophils and basophils (♀) – ↑ plasma gamma-glutamyl transferase (♂) – ↓ glucose (♀) – ↓ water consumption (♀)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
90-day Dietary **NOA 447204 (M3)**	12/sex/dose Alpk:AP$_f$SD rats **Dose Levels:** 0, 150, 1000, 6000 ppm (0/0, 15.0/15.2, 99.2/98.8 and 600.6/645.4 mg/kg bw/day for ♂/♀)	**NOAEL** = 1000 ppm **LOAEL** = 6000 ppm	**6000 ppm** – ↓ body-weight gain and food efficiency (♂,♀) – ↓ water consumption (♀) – ↑ gamma-glutamyl transferase (♂,♀) – ↓ triglycerides (♂) – ↑ cholesterol (♀) – ↑ absolute and relative (to terminal body weight) liver weights (♂,♀) – Enlarged livers (♂) – Minimal to moderate panlobular reduced glycogen/increased eosinophilia in the liver (♂,♀) – ↑ proteinuria (♂) – ↑ incidence and severity of ketonuria (♂) – ↑ absolute and relative kidney weight (♂) – Minimal chronic progressive nephropathy (♂) Terminal Body Weights: 528.8g/278.3g (♂,♀) Food Consumption: 29.5g/18.4g study average
28-day Dietary (supplemental, non-guideline) **SYN 502836 (M6)**	5/sex/dose Alpk:AP$_f$SD rats **Dose Levels:** 0, 300, 3000, 6000 and 12 000 ppm (0/0, 33.8/33.6, 334.2/328.2, 659.3/626.8 and 1309.6/1286.9 for ♂/♀) (limit dose)		No adverse effects
90-day Dietary **SYN 502836 (M6)**	12/sex/dose Alpk:AP$_f$SD rats **Dose Levels:** 0, 300, 3000 and 12 000 ppm (0/0, 23.9/26.8, 246.8/266.4 and 977.5/1034.9 mg/kg bw/day for ♂/♀) (limit dose)	**NOAEL** = 12 000 ppm **LOAEL** = not observed	No adverse effects Terminal Body Weights: 386.2g/241.6g (♂,♀) Food Consumption: 28.7g/19.0g (♂,♀)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
CHRONIC TOXICITY AND ONCOGENICITY			
78-week Gavage	70/sex/dose CD-1 mice **Dose Levels:** 0, 5, 40, 300 and 750 mg/kg bw/day	NOAEL and LOAEL not determined Gavage errors and lung involvement made interpretation of results impossible.	**≥ 40 mg/kg bw/day** – Minimal to marked congestion in the lung, liver and kidney (♂) – ↑ incidence and severity of hyalinosis in lungs (♂) **≥ 300 mg/kg bw/day** – ↓ body-weight gain (♀) – ↓ food efficiency (♂,♀) – Minimal to marked congestion in the lung, liver and kidney (♀) – ↑ relative (to body) liver weight (♂,♀) – Minimal to marked glycogen deposition in liver (♂,♀) – Pus in nose (♂) – Pus in nose, inflammatory cell infiltration and purulent infiltration (♀) **≥ 750 mg/kg bw/day** – ↓ body-weight gain (♂) – ↑ water consumption (♂,♀) – Tonic convulsions (♂) – Piloerection (♂,♀) – Hunched posture (♀) – Slight to moderate congestion in the adrenal gland (♂) – ↑ incidence of hyalinosis in lungs (♀) – ↑ absolute liver weight (♂,♀) – ↑ incidence of minimal to slight tubular atrophy and minimal to moderate casts in the kidney (♀)
80-week Dietary	50/sex/dose CD-1 mice **Dose Levels:** 0, 150, 500, 1500 and 4000 ppm (0/0, 16.3/20.2, 60.7/75.7, 181.2/216.5 and 573.7/706.4 for ♂/♀)	**NOAEL =** 1500 ppm (181/216 mg/kg bw for ♂/♀) **LOAEL** not observed Maximum tolerated dose not reached.	**4000 ppm** – Terminated week 40 due to ↓ body-weight gain No treatment related effects at any dose

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
2-year Gavage	80/sex/dose HanIbm:WIST rats (10/sex/dose interim group) **Dose Levels:** 0, 1, 10, 100, 250 and 500 mg/kg bw/day	**NOAEL** = 100 mg/kg bw/day **LOAEL** = 250 mg/kg bw/day No evidence of carcinogenicity	**10 mg/kg bw/day** – One ♀ had a leiomyosarcoma in the stomach **100 mg/kg bw/day** – One ♂ had a leiomyosarcoma in the spleen **≥ 250 mg/kg bw/day** – ↓ body weight, body-weight gain and ↑ water consumption (♂,♀) – ↓ incidence of survival (♂) – ↑ incidence of hunched posture and piloerection (♂) – ↓ serum glucose (♂,♀) – ↑ serum urea and creatinine (♂) – ↑ urine volume (♂,♀) – ↑ incidence of surface granulation in the kidney at interim and terminal sacrifice (♂) – ↑ incidence and severity of chronic nephropathy in males at week 105 (♂) - ↑ incidence and severity of renal pelvis dilation at week 105 (♀) – ↑ incidence and/or severity of fibrous osteodystrophy and parathyroid hyperplasia (♂) – ↑ relative (to body) thyroid and parathyroid weight – ↑ incidence (2/60) of leiomyosarcoma in the stomach (♂) **500 mg/kg bw/day** – ↑ incidence of surface granulation of kidney week 53 (♀) – ↑ epithelial cells in urine (♂,♀) – ↑ absolute and relative (to body) kidney weight week 53 (♂) – Termination at week 61 due to ↑ in spontaneous deaths (♂) – ↑ serum urea and creatinine (♀) – ↑ incidence of chronic nephropathy, renal tubular vacuolation and renal cysts week 105 (♀)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
REPRODUCTION AND DEVELOPMENTAL TOXICITY			
Multigeneration	30/sex/dose HanIbm:WIST rats **Dose Levels:** 0, 10, 50, 250, 500 mg/kg bw/day	**Parental** **NOAEL =** 250 mg/kg bw/day **LOAEL =** 500 mg/kg bw/day	**Parental** **500 mg/kg bw/day** – ↑ water consumption (P and F_1 ♂) – ↑ water consumption during premating (♀) – ↑ absolute and relative (to body) kidney weight (P and F_1 ♂) – ↑ incidence of slight to marked dilation of the renal pelvis (P ♂) – ↑ incidence of minimal to moderate renal tubular atrophy (P and F_1 ♂) – ↑ incidence of minimal to moderate renal tubular atrophy (P ♀) – ↑ incidence of minimal to moderate chronic nephropathy (P and F_1 ♀)
		Offspring **NOAEL =** 250 mg/kg bw/day **LOAEL =** 500 mg/kg bw/day	**Offspring** **500 mg/kg bw/day** – ↓ body weight (F_1 and F_2 ♂, F_1 ♀) – ↓ body-weight gain (F_1 ♂,♀)
		Reproductive **NOAEL =** 500 mg/kg bw/day **LOAEL** not observed	**Reproductive** No adverse effects
Developmental toxicity (rodent) Range-finding, non-guideline	8 female/dose HanIbm:WIST rats **Dose Levels:** 0, 30, 300, 700 and 1000 mg/kg bw/day		**Maternal** **1000 mg/kg bw/day** – Piloerection GD 15–21 **≥700 mg/kg bw/day** – ↓ body-weight gain both when corrected and uncorrected for gravid uterine weight – ↓ food consumption **Developmental** **≥700 mg/kg bw/day** – ↓ body weights (♂,♀)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Developmental Toxicity (rodent)	24 females/dose HanIbm:WIST rats **Dose Levels:** 0, 3, 30, 300 and 800 mg/kg bw/day	**Maternal** NOAEL = 30 mg/kg bw/day LOAEL = 300 mg/kg bw/day	**Maternal** **≥ 300 mg/kg bw/day** – ↓ body-weight gains – ↓ food consumption **800 mg/kg bw/day** – ↓ body-weight gain both when corrected and uncorrected for gravid uterine weight – ↓ gravid uterine weight – 1 dam killed for humane reasons GD 17 – ↑ incidence of piloerection GD 15–21
		Developmental NOAEL = 30 mg/kg bw/day LOAEL = 300 mg/kg bw/day	**Developmental** **≥300 mg/kg bw/day** – incomplete ossification of the interparietal and metatarsal 1 **800 mg/kg bw/day** – ↑ incidence of incomplete ossification of occipital, parietal and frontal bones and unossified hind limb calcaneus, metatarsal 1 and the distal phalanx of posterior digits 2, 3 and 4 – ↓ in fetal body weight (♂,♀) **Not teratogenic**

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Developmental Toxicity (non-rodent) Range-finding, non-guideline	8 females/dose Russian Chbb:HM rabbits **Dose Levels:** 0, 30, 150, 300, 700 and 1000 mg/kg bw/day		**Maternal** **≥30 mg/kg bw/day** – ↓ body-weight gains, food consumption **≥150 mg/kg bw/day** – 1 doe killed for humane reasons – ↓ food consumption **≥300mg/kg bw/day** – 1 female died GD 18 – Group terminated due to hunched posture, reduced activity, severe body-weight loss **≥700 mg/kg bw/day** – 3 females found dead GD 11–12 – Group terminated due to hunched posture, reduced activity, severe body-weight loss **1000 mg/kg bw/day** – 2 females found dead GD 8–9 – Group terminated due to hunched posture, reduced activity, severe body-weight loss **Developmental** **150 mg/kg bw/day** – fetal body weight (♂,♀) – 4/8 does had complete litter resorptions – ↑ early resorption per doe – ↑ postimplantation loss
Developmental Toxicity (non-rodent)	24 females/dose Russian Chbb:HM rabbits **Dose Levels:** 0, 3, 10, 30 and 100 mg/kg bw/day		**Maternal** **100 mg/kg bw/day** – ↓ body-weight gain – ↓ decreased body-weight gain for both uncorrected and corrected for gravid uterine weight – ↓ food consumption **Developmental** **100 mg/kg bw/day** – ↓ fetal body weights (♂,♀) – 1 dead fetus observed – Diaphragmatic hernia (1/sex) – Fissure of diaphragm (1 ♂) **30 mg/kg bw/day** – Diaphragmatic hernia (1 ♀)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Developmental Toxicity (non-rodent) Supplemental non-guideline	24 females/dose Russian Chbb:HM rabbits Using one male control (Buck 119) **Dose Levels**: 0, 100 mg/kg bw		**Maternal** **100 mg/kg bw/day** – One female euthanized following abortion GD 26 – ↓ body weights (both when uncorrected and corrected for gravid uterus weight) – ↓ body-weight gain, food consumption **Developmental** No adverse effects
Developmental Toxicity (non-rodent) Supplemental non-guideline	24 females/dose Russian Chbb:HM rabbits Using 12 males (not Buck 119) **Dose Levels**: 0, 100 mg/kg bw/day		**Maternal** **100 mg/kg bw/day** – One female found dead GD 23 – ↓ body weights (both when uncorrected and corrected for gravid uterus weight) – ↓ body-weight gain, food consumption **Maternal and Developmental** **100 mg/kg bw/day** – One dam was euthanized following abortion GD 27 – 2 females had complete litter resorptions – 19 early resorptions were observed causing ↑ postimplantation losses (15 from the complete litter resorptions) **Not teratogenic**
Developmental Toxicity (non-rodent)	24 females/dose Russian Chbb:HM rabbits **Dose Levels:** 0, 3, 10, 30 and 100 mg/kg bw/day	**Maternal** **NOAEL** = 30 mg/kg bw/day **LOAEL** = 100 mg/kg bw/day **Developmental** **NOAEL** = 30 mg/kg bw/day **LOAEL** = 100 mg/kg bw/day	**Maternal** **100 mg/kg bw/day** – 1 female euthanized GD 26 for humane reasons – 2 females euthanized GD 27 after showing signs of abortion – ↓ body-weight gain for uncorrected gravid uterus weight – ↓ food consumption – ↓ body weight **Developmental** **100 mg/kg bw/day** – ↑ total and early litter resorptions and postimplantation loss – 3 dead fetuses – 2 abortions **Not teratogenic**

STUDY	SPECIES and STRAIN or CELL TYPE AND CONCENTRATIONS or DOSES	RESULTS
GENOTOXICITY PINOXADEN		
Gene Mutations in Bacteria	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537; *E. Coli* WP2uvrA 33, 100, 333, 1000, 2500 and 5000 µg/plate; with and without activation (limit dose)	Negative
Gene Mutations in Mammalian Cells in vitro	Mouse lymphoma cell (L5178Y TK$^{+/-}$ locus) 6.3, 12.5, 25, 50, 100 200, 300 and 400 µg/mL without activation 3.1, 6.3, 12.5, 25, 50, 100 and 150 µg/mL with activation	Negative
Unscheduled DNA Synthesis (in vivo)	Primary rat hepatocytes (male SD rats) 2000 mg/kg (single oral dose; primary cultures scored for unscheduled DNA synthesis 2–4 and 12–16 hours after dose administration)	Negative
Chromosome Aberrations in vitro	V79 Chinese hamster lung fibroblasts 6 trials, each with 6 doses ranging from 6.3 to 120 µg/mL and different exposure times	Positive – In the presence (≥60µg/mL) and absence (≥25µg/mL) of S9 Cytotoxic ≥80µg/mL +S9, ≥80µg/mL -S9 **Clastogenic**
Chromosome Aberrations in vitro	V79 Chinese hamster lung fibroblasts 6 trials, each with 6 doses ranging from 3.8 to 100 µg/mL and different exposure times	Positive – In the presence (≥45µg/mL) and absence (≥90µg/mL) of S9 Cytotoxic ≥45µg/mL +S9, ≥75µg/mL -S9 **Clastogenic**
Unscheduled DNA Synthesis in vitro	Primary rat hepatocytes (male SD rats) 0, 1.17, 2.34, 4.69, 9.38, 18.75, 37.5, 75, 150, 300 or 600 µg/mL	Negative
Micronucleus Assay (in vivo)	Male and female CD-1 (ICR) mice 0, 500, 1000 or 2000 mg/kg (single oral dose; bone marrow harvested 24 and 48 hours postdosing) (limit dose)	Negative
GENOTOXICITY: METABOLITE of PINOXADEN (NOA 447204) (M3)		
Gene Mutations in Bacteria	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; *E. Coli* WP2uvrA and WP2 100, 200, 500, 1000, 2500 and 5000 µg/plate; with and without activation (limit dose)	Negative
Gene Mutations in Mammalian Cells in vitro	Mouse lymphoma cell (L5178Y TK$^{+/-}$ locus) 125, 250, 500, 750, 1000, 1500, 2000 and 3325 µg/mL without activation 125, 250, 500, 750, 1000, 1500, 2000 and 3324 µg/mL with activation	Negative

STUDY	SPECIES and STRAIN or CELL TYPE AND CONCENTRATIONS or DOSES	RESULTS
Unscheduled DNA Synthesis (in vivo)	Primary rat hepatocytes (male SD rats) 0, 625 and 1250 mg/kg (single oral dose; primary cultures scored for unscheduled DNA synthesis 2 and 16 hours after dose administration)	Negative
Chromosome Aberrations in vitro	Human lymphocyte (peripheral blood) 50, 100, 250, 500, 750, 1000, 1500, 2000, 2500, 3000 and 3324 µg/mL without activation 50, 100, 250, 500, 750, 1000, 1500, 2000, 2500, 3000 and 3324 µg/mL with activation	Positive – In the presence (≥ 1500 µg/mL) and absence (≥ 1500 µg/mL) of S9 Cytotoxic ≥ 1500 µg/mL +S9, ≥ 500 µg/mL -S9 **Clastogenic**
Micronucleus Assay (in vivo)	Male CD-1 (ICR) mice 0,200, 400 and 800 mg/kg (single oral dose; bone marrow harvested 24 and 48 hours postdosing)	Negative
GENOTOXICITY: METABOLITE of PINOXADEN (SYN 502836) (M6)		
Gene Mutations in Bacteria	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; *E. Coli* WP2uvrA and WP2 100, 200, 500, 1000, 2500 and 5000 µg/plate; with and without activation (limit dose)	Negative
Gene Mutations in Mammalian Cells in vitro	Mouse Lymphoma Cell (L5178Y $TK^{+/-}$ locus) 125, 250, 500, 1000, 1500 and 2000 µg/mL without activation 125, 250, 500, 1000, 1500 and 2000 µg/mL with activation	Negative
Chromosome Aberrations in vitro	Human lymphocyte (peripheral blood) 50, 100, 200, 500, 1000, 1500, 2000 and 2750 µg/mL without activation 50, 100, 200, 500, 1000, 1500, 2000 and 2750 µg/mL with activation	Negative
GENOTOXICITY: METABOLITE of PINOXADEN (SYN 505887) (M10)		
Gene Mutations in Bacteria	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; *E. Coli* WP2uvrA and WP2 100, 200, 500, 1000, 2500 and 5000 µg/plate; with and without activation (limit dose)	Negative
Gene Mutations in Mammalian Cells in vitro	Mouse Lymphoma Cell (L5178Y $TK^{+/-}$ locus) 125, 250, 500, 1000, 2000 and 3484 µg/mL without activation 125, 250, 500, 1000, 2000 and 3484 µg/mL with activation	Positive – In the absence (≥2000 µg/mL) of S9 No cytotoxicity. forward gene mutation

STUDY	SPECIES and STRAIN or CELL TYPE AND CONCENTRATIONS or DOSES	RESULTS
Unscheduled DNA Synthesis (in vivo)	Primary rat hepatocytes (male SD rats) 2000 mg/kg (single oral dose; primary cultures scored for unscheduled DNA synthesis 2 and 16 hours after dose administration)	Negative
Chromosome Aberrations in vitro	Human lymphocyte (peripheral blood) 10, 50, 100, 250, 500, 750, 1000, 1500, 2500 and 3484 μg/mL without activation 10, 50, 100, 250, 500, 750, 1000, 1500, 2500 and 3484 μg/mL with activation	Negative
Micronucleus Assay (in vivo)	Male CD-1 (ICR) mice 2000 mg/kg (single oral dose; bone marrow harvested 24 and 48 hours postdosing) (limit dose)	Negative
GENOTOXICITY: METABOLITE of PINOXADEN (SYN 519312)		
Gene Mutations in Bacteria	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; *E. Coli* WP2uvrA and WP2 100, 200, 500, 1000, 2500 and 5000 μg/plate; with and without activation (limit dose)	Negative

SPECIAL STUDIES

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Acute Dietary Neurotoxicity (supplemental, non-guideline)	3/sex/dose Wistar rats **Dose Levels:** 0, 2000 mg/kg bw (limit dose)	**NOAEL** > 2000 mg/kg bw **LOAEL** not observed	No adverse effects
Acute Dietary Neurotoxicity	10/sex/dose Wistar rats **Dose Levels**: 0, 100, 500 and 2000 mg/kg bw (limit dose)	**NOAEL** > 2000 mg/kg bw **LOAEL** not observed	No adverse effects
90-day Dietary Neurotoxicity	12/sex/dose Wistar rats **Dose Levels:** 0, 10, 100 and 500 mg/kg bw/day	**NOAEL** > 500 mg/kg bw/day **LOAEL** not observed	No adverse effects
Developmental Neurotoxicity	Waiver request: Waiver request was based on a lack of evidence of neurotoxicity, a lack of evidence for developmental toxicity, a lack of evidence of reproductive effects or increased sensitivity of offspring and a lack of evidence in the toxicology studies that would be indicative of neurotoxic effects. Waiver **GRANTED**		

Compound-Induced Mortality: In the 90-day capsule study in dogs, all females at the 500 mg/kg bw/day dose group were sacrificed week 5 for humane reasons. In the 78-week dietary mouse study, all animals in the 4000 ppm dose group were sacrificed week 40 due to decreased body-weight gain. In the 2-year gavage rat study, all males in the 500 mg/kg bw/day dose group were sacrificed week 61 due to an increase in spontaneous deaths. In the rodent developmental study, 1 dam in the 800 mg/kg bw/day dose group was killed for humane reasons GD 17. In a range-finding developmental toxicity study conducted in rabbits, 1 female in the 300 mg/kg bw/day dose group died GD 18, 3 females died between GD 11–12 in the 700 mg/kg bw/day dose group and 2 females died between GD 8–9 in the 1000 mg/kg bw/day dose group. In two of the rabbit developmental studies, dead fetuses were observed at the 100 mg/kg bw/day dose (1 in one study and 3 in another). In a third rabbit developmental toxicity study, one dam was found dead GD 23 in the 100 mg/kg bw/day dose group.

Recommended Acute Reference Dose: for Females 13+ is 0.1 mg/kg bw/day based on a NOAEL of 30 mg/kg bw/day from developmental rabbit study with an uncertainty factor of 300. (100 for interspecies and intraspecies and 3× for severity of effect—resorptions)

Recommended Acceptable Daily Intake is 0.1 mg/kg bw/day based on a NOAEL of 30 mg/kg bw/day from developmental rabbit study with an uncertainty factor of 300. (100 for interspecies and intraspecies and 3× for severity of effect—resorptions)

Toxicological Endpoints for Occupational Risk Assessment: For the short-term dermal route, the rabbit developmental toxicity study with a NOAEL of 30 mg/kg bw/day was considered most appropriate with an increased incidence of complete early litter resorptions at the LOAEL of 100 mg/kg bw/day. A safety factor of 300 was added (100× for interspecies and intraspecies and 3× for severity of effect—resorptions).

Appendix II Residues

Direction for Use

Crop	Formulation Type	Application/ Season	Rate (g a.i./ha)	Growth Stage (BBCH)	PHI	Pregrazing Interval	Adjuvant**
Spring Wheat, Durum Wheat and Barley	Emulsifiable concentrate	1	40–60	1- to 6-leaf, prior to fourth tiller* (11-20 to 16-23)	60 days for grain and straw	7 days	ADIGOR (A12127S formulation) or Merge (700 mL/ha)

* Do not apply past the flag leaf stage.

** Do not tank mix with any other adjuvants, chemical additives, pesticides or fertilizers unless recommended on the label.

For use in the Prairie Provinces as well as the Peace River, Okanagan and Creston Flats regions of British Columbia.

Label Recommendations:

PHI of 30 days for hay

Crop Rotation Restrictions:
– 0 day for wheat and barley
– 30 days for all the other crops not listed on the label

Physicochemical Properties

Water solubility	200 mg/L at 25°C
Solvent solubility at 25°C (g/L)	Acetone 250 Dichloromethane >500 Ethyl acetate 130 Hexane 1.0 Methanol 260 Octanol 140 Toluene 130
n-Octanol–water partition coefficient (Log $_{K_{ow}}$)	3.2 at 25°C
Vapour pressure	2.0×10^{-7} Pa at 20°C 4.6×10^{-7} Pa at 25°C
Relative density	1.16×10^{3} kg/m^{3} at 24°C
Melting point	120.5–121.6°C
UV–Visible absorption spectrum	**Conditions** λ_{max} Neutral solution 210, 258 Acidic solution 210, 254 Basic solution 220, 252 No absorption maximum between 350 and 750 was observed in any of the three solutions.

Analytical Methodology

Parameters	Plant Matrices
Method ID	REM 199.02
Type	Data-gathering method
Analytes	M2 (NOA 407854), M4 (SYN 505164), M6 (SYN 502836) and M10 (SYN 505887)
Instrumentation	HPLC-MS/MS (with column switching systems)
LOQ	0.01 ppm for cereal grain 0.02 ppm for cereal whole plants, ears, stalks and straw
Standard	External standardization.
ILV	No ILV submitted.
Extraction/clean-up	Extraction: 1N HCl under reflux for two hours. Clean-up: If solution not clear through a filter paper or a membrane filter Acrodisc LC 13.
Method ID	REM 199.03
Type	Data-gathering method
Analytes	M2 (NOA 407854), M4 (SYN 505164), M6 (SYN 502836) and M10 (SYN 505887)
Instrumentation	HPLC-MS/MS
LOQ	0.01 ppm for cereal grain 0.02 ppm for cereal whole plants, ears, stalks and straw
Standard	External standardization.
ILV	No ILV submitted.
Extraction/clean-up	Extraction: 1N HCl under reflux for two hours. Clean-up: Filtration using a Vectaspin filtration tube Oasis HLB SPE clean-up (elution with dichloromethane/ethyl acetate/formic acid [80:20:0.5, v/v/v]).
Method ID	117-01
Type	Data-gathering and enforcement method
Analytes	M2 (NOA 407854), M4 (SYN 505164) and M6 (SYN 502836)
Instrumentation	HPLC-MS/MS (with column switching systems)
LOQ	0.01 ppm for cereal grain 0.02 ppm for cereal forage, hay and straw
Standard	External standardization.
ILV	The independent laboratory, successfully validated Method 117-01 at the first or second attempt using wheat (forage, straw, grain and aspirated grain fractions) and barley (hay and grain) matrices.
Extraction/clean-up	Extraction: 1N HCl (or 1N HCl/acetonitrile [90:10, v/v]) under reflux for two hours. Clean-up: **For M4 and M6 only** The extract was cleaned up with a preconditioned SCX (2) SPE cartridge (elution with acetonitrile/water [25:75, v/v]) followed by a preconditioned C_8 SPE column (elution with acetonitrile/0.2% formic acid [50:50, v/v}].

Multiresidue methods (MRMs)	MRM protocols A through G of the *Pesticide Analytical Manual* Vol. I **are not suitable** for the analysis of pinoxaden and the metabolites M2, M4, M6 and M10.
Parameters	**Animal Matrices**
Method ID	T001530-03
Type	Data-gathering and enforcement method
Analytes	M4 (SYN 505164) and M6 (SYN 502836)
Instrumentation	HPLC-MS/MS
LOQ	0.02 ppm for each analyte in tissues and eggs 0.01 ppm for each analyte in milk
Standard	External standardization
ILV	The independent laboratory successfully validated Method T001530-03 using beef muscle, beef fat, milk and eggs on the first attempt.
Extraction/clean-up	Extraction: 1N HCl under reflux for two hours. Clean-up: SCX (2) cartridge (elution with acetonitrile/water [5:25, v/v]) followed by C_8 cartridge (elution with acetonitrile/0.2% formic acid [50:50, v/v]).
Nature of the Residue in Wheat	
Radiolabel	[Pyrazol-3,5-$^{14}C_1$] pinoxaden, [Phenyl-1-^{14}C] pinoxaden or [Oxadiazepin-3,6-$^{14}C_1$] pinoxaden
Test site	Under outdoor conditions.
Treatment/rate	**Field Experiment I** Pinoxaden formulated as an emulsifiable concentrate (EC 200; formulation EZA14086) containing the safener cloquintocet-mexyl ([(5-chloro-8-quinolinyl)-oxy]-acetic acid 1-methylhexyl ester) was applied as a fall application to winter wheat plants at growth stage BBCH 13 (three leaves unfolded) as a foliar spray at a rate of 68.5 g a.i./ha. No adjuvant was added to the spray mixture. **Field Experiment II** Pinoxaden formulated as an emulsifiable concentrate (EC 120; formulation A12413A) containing the safener cloquintocet-mexyl was applied as a spring application to winter wheat plants at growth stage BBCH 49 (first awns visible) as a foliar spray at a rate of either 64 g a.i./ha or 318 g a.i./ha. The adjuvant Merge was added to the spray mixture. **Field Experiment III** Pinoxaden formulated as an emulsifiable concentrate (EC 100; formulation A-12303C) containing the safener cloquintocet-mexyl was applied as an early season application to spring wheat plants at growth stage BBCH 21 (initial tillering) as a foliar spray at a rate of 60.0 g a.i./ha for the phenyl radiolabel study and at 58.1 g a.i./ha for the oxadiazepine radiolabel study. The adjuvant A-12727 M was added to the spray mixture. **Field Experiment IV** Pinoxaden was applied as an emulsifiable concentrate (EC 100; formulation A-12303C) containing the safener cloquintocet-mexyl to spring wheat plants at growth stage BBCH 37-39 (flag leaf just visible to flag leaf fully unrolled) as a foliar spray at a rate of 62.0 g a.i./ha for the phenyl radiolabel study and at 66.0 g a.i./ha for the oxadiazepine radiolabel study. The adjuvant A-12727M was added to the spray mixture.

PHI	**Field Experiment I** Wheat forage was harvested immediately following application (0-day PHI), 14 days, 42 days and 209 days after treatment. Mature wheat was collected 264 days after treatment and was divided into grain, husk and straw fractions. **Field Experiment II** Wheat forage (whole tops) was harvested immediately following application (0-day PHI), 7 days and 14 days after treatment. Tops and ears were collected at a 28-day PHI. Mature wheat was harvested 55 days after treatment and was divided into grain, husk and straw fractions. **Field Experiment III** Wheat forage (whole tops) was harvested immediately following application (0 DAT), 14 days and 28 days after treatment. **Field Experiment IV** Wheat forage (whole tops) was harvested immediately following application (0 DAT), 7 days, 14 days and 28 days after treatment. Ears were collected at a PHI of 28 days. Mature wheat was harvested 67 days after treatment and was divided into grain, husk and straw fractions.					
Metabolites Identified	Major Metabolites (>10% TRRs)			Minor Metabolites (<10% TRRs)		
Radiolabel	Pyrazol	Phenyl	Oxadiazepine	Pyrazol	Phenyl	Oxadiazepine
0-DAT forage	Pinoxaden M2	Pinoxaden M2 M4	Pinoxaden M2	M3	M3 M5 M6 M11	M3 M4 M6
7-DAT forage	—	M4 M5	M4 M5	—	Pinoxaden M2 M3 M6 M7 M8 M10	Pinoxaden M2 M3 M6 M8
14-DAT forage	M4 M5	M4 M5 M6	M4 M5	Pinoxaden M2 M3 M6 M7 M8 M9 M10 M11	Pinoxaden M2 M3 M7 M8 M9 M10 M11 M14	Pinoxaden M2 M3 M6 M7 M8 M9 M10 M11 M14
28-DAT forage	—	M5	M5	—	M2 M3 M4 M6 M7 M8 M9 M10 M11 M14	M3 M4 M6 M7 M8 M9 M11

Radiolabel	Pyrazol	Phenyl	Oxadiazepine	Pyrazol	Phenyl	Oxadiazepine
42-DAT forage	M5 M9	—	—	M2 M3 M4 M6 M7 M8 M11	—	—
209-DAT forage	M3 M8	—	—	M4 M9 M10 M11 M32	—	—
28-DAT tops	—	M5	M5	—	M3 M4 M6 M7 M8 M9 M10	M3 M4 M6 M7 M8 M9 M14
28-DAT ears	—	M4 M5	M4 M5 M6	—	M6 M8 M9 M14	M3 M9 M14
Mature grain (55 or 67 DAT)	M4 M6	M4 M5 M6 M7	M5 M6	M5 M7 M10	M8 M10	M4 M7
55- or 67-DAT husks	—	M4 M5	M4 M6	—	M3 M6 M7 M8 M9 M10 M11 M14 M31 M32	M3 M5 M6 M7 M9 M10 M11 M32
209-DAT husks	M3 M10	—	—	M4 M8 M11 M32	—	—
55- or 67-DAT straw	—	M4 M10	M4	—	M3 M5 M6 M7 M8 M10 M11 M14 M31 M32	M3 M5 M6 M9 M10 M11 M32

Radiolabel	Pyrazol	Phenyl	Oxadiazepine	Pyrazol	Phenyl	Oxadiazepine
209-DAT straw	M3 M10	—	—	M4 M8 M11 M32	—	—

Radiolabel	[Pyrazol-3,5-$^{14}C_1$] pinoxaden
Test site	Cell culture experiment.
Treatment/rate	Cell suspensions of a stock solution of wheat cells were used to conduct this experiment. Following subculturing, the cells were grown for 6 days prior to treatment. Solutions of various concentrations of [pyrazol-3,5-$^{14}C_1$] pinoxaden, with and without the safener, were mixed with the cell suspension.
PHI	Samples of the cell culture were taken 2 and 9 days after treatment.

Two days after treatment, the cell culture medium accounted for 66% of the applied radioactivity and the cell extract for 19%. The purified isolated fractions that had been assigned a chemical structure were used as reference compounds for TLC co-chromatography with the corresponding fraction observed in the field experiment.

Metabolites Identified	Major Metabolites
Radiolabel	Pyrazol
Culture medium (day 2)	M2 M4
Culture medium (day 9)	M4 M5
Cell extract (day 2)	M2 M4 M5 M6
Cell extract (day 9)	M4 M5 M6 M7

Radiolabel	[Pyrazol-3,5-$^{14}C_1$] pinoxaden
Test site	Stem injection experiment: under greenhouse conditions for first month then in a growth chamber.
Treatment/rate	When wheat reached the early booting stage (BBCH 41), plant stems were treated by means of a syringe injection (approximately 1–2 cm above first node) with a pinoxaden solution (representing a rate of 1 176 000 dpm/μL) containing the safener cloquintocet-mexyl.
PHI	Sampling was comprised of whole tops (forage) collected 14 DAT, ears and stalks with leaves collected 28 DAT and mature wheat (grain, husk and straw) collected 56 DAT.

Total Radioactive Residues
The TRRs were 1.520 ppm in wheat grain, 5.820 ppm in wheat husk and 34.344 ppm in wheat straw.

Metabolites Identified	Major Metabolites (>10% TRRs)	Minor Metabolites (<10% TRRs)
Radiolabel	Pyrazol	Pyrazol
Grain (56 DAT)	M6 M7	M4 M5
Husks (56 DAT)	M5	M3 M4 M6 M7 M8 M10
Straw (56 DAT)	M2 M4	M3 M5 M6 M8 M9 M10 M11 M31 M32

Confined Rotational Crop Study—Lettuce, Mustard Leaves, Radish, Turnip and Wheat	
Radiolabels	[Phenyl-1-^{14}C] pinoxaden or [Oxadiazepin-3,6-$^{14}C_1$] pinoxaden
Test site	Under outdoor conditions
Treatment	Formulation applied once to bare soil
Rate	60–70 g a.i./ha
PBI	Soil was aged for 15, 30, 120, 170 and 365 days after treatment. Crops were harvested at maturity.

Total radioactive residues (TRRs) accumulated at levels greater than 0.01 ppm in mustard leaves, turnip tops, wheat forage and wheat fodder planted 15 days after treatment. TRRs also exceeded 0.01 ppm in lettuce, radish tops, wheat forage and wheat fodder planted 29–30 days after treatment.

At the 15-DAT plantback interval, none of the metabolites identified (M3, M8, M10, conjugates of M10 [ME2, ME3 and ME5] and M11) were quantitated at levels greater that 0.01 ppm, except M3, M10 and M11 in spring wheat fodder (both radiolabels). Wheat fodder is considered a feed item.

At the 29–30 DAT plantback interval, none of the metabolites identified (M2, M3, M8, M9, M10, M11 and M32) were quantitated at levels greater that 0.01 ppm, except M3 in spring wheat forage (0.024 ppm; oxadiazepine radiolabel study only). Wheat forage is considered a feed item.

Pinoxaden was not detected in any rotated crop matrices at any PBI (from 15 to 365 days). Throughout the three confined rotational crop studies, no substantive variation in the metabolic degradation of pinoxaden was observed. Pinoxaden was hydrolyzed rapidly (disappeared by Day 3) in soil yielding M2. M2 was further hydroxylated forming M3 the predominant metabolite observed in soil.

The metabolic profile of ^{14}C-pinoxaden in wheat (primary crop) was similar to the metabolic profiles observed in the rotational studies for wheat, lettuce, mustard leaves, radish and turnip (secondary crops).

The data support a plantback interval of 0 day for wheat and barley and of 30 days for all the other crops.

The results from the confined accumulation study did not trigger the need for a field accumulation study.

Nature of the Residue in Lactating Goat

Species	Radiolabel	Dose Level	Length of Dosing	Sacrifice
Caprus hircus Alpine breed	[Phenyl-1-^{14}C]pinoxaden	120.6 ppm in feed	4 consecutive days	~6 hours after final dose

Approximately 66.8% of the AD was recovered in the excreta (feces, urine and cage wash), with an additional 18.5% of the AD recovered in gastrointestinal tract and rumen. Only 0.009% of the AD was transferred into milk and less than 0.3% of the AD was transferred to edible tissues.

TRRs were 0.015 ppm in milk (0–78 h), 0.081 ppm in leg muscle, 0.075 in tenderloin muscle, 0.016 ppm in omental fat, 0.021 ppm in perirenal fat, 2.953 in kidney, 1.160 ppm in liver, 0.201 ppm in blood and 53.10 ppm in bile.

Metabolites Identified	Major Metabolites (>10% TRRs)	Minor Metabolites (<10% TRRs)
Radiolabel	[Phenyl-1-^{14}C] Pinoxaden	
Milk	M2	M3 M4 M12
Muscle	M2	M4 M12
Fat	M2	M4 M12
Liver	M2	M4 M12
Kidney	M2	M3 M4 M12 M13

Species	Radiolabel	Dose Level	Length of Dosing	Sacrifice
Caprus hircus Alpine breed	[7-^{14}C] M4	9.8 ppm in feed	4 consecutive days	~6 hours after final dose

The majority of the AD was excreted, via feces (60.18% of the AD) and urine (9.10% of the AD). An additional 23.61% of the AD was recovered from the contents of the gastrointestinal tract. Residues in milk accounted for less than 0.002% of the AD, while less than 0.1% of the AD was transferred to tissues.

In urine, TRRs were 0.761 ppm (0–24 h), 0.789 ppm (24–48 h), 1.071 ppm (48–72 h) and 0.945 ppm (72–78 h). In feces, TRRs were 6.841 ppm (0–24 h), 12.379 ppm (24–48 h), 13.292 ppm (48–72 h) and 9.121 ppm (72–78 h). TRRs in milk at all sampling intervals were less than 0.002 ppm (<LOQ). TRRs were <0.011 ppm (<LOQ) in muscle, fat and blood, 0.044 ppm in kidney, 0.025 ppm in liver, 0.497 ppm in bile and 1.202 ppm in the gastrointestinal tract.

Metabolites Identified	Major Metabolites (>10% TRRs)	Minor Metabolites (<10% TRRs)
Radiolabel	[7-^{14}C] M4	
Kidney	M4	M10
Liver	M4	M10

Nature of the Residue in Laying Hen

Species	Radiolabel	Dose Level	Length of Dosing	Sacrifice
Gallus gallus domesticus White Leghorn Hyline W-98 breed	[Phenyl -1-^{14}C] pinoxaden	96.7 ppm in feed	4 consecutive days	~6 hours after final dose

Approximately 75% of the AD was eliminated in excreta, with an additional 10% of the AD recovered in the gizzard. Only minor fractions of the total AD were transferred to eggs (0.007%) and edible tissues (0.158%).

TRRs in egg whites were 12 ppb (0–24 h), 15 ppb (24–48 h), 13 ppb (48–72 h) and13 ppb (72–78 h), while TRRs in egg yolks were 0 ppb (0-24 h), 22 ppb (24-48 h), 48 ppb (48-72 h) and 31 ppb (72-78 h). TRRs were 60 ppb in lean muscle, 161 ppb in skin with attached fat, 32 ppb in peritoneal fat, 1782 ppb in kidney, 617 ppb in liver and 306 ppb in blood.

Metabolites Identified	Major Metabolites (>10% TRRs)	Minor Metabolites (<10% TRRs)
Radiolabel	[Phenyl-1-^{14}C] Pinoxaden	
Egg white	M2 M4	M33 M34 M35
Egg yolk	M4 M6	M2 M33 M34 M35
Lean muscle	M2 M4 M6	M33 M34
Fat and skin	M4 M6	M2 M31 M33 M34 M35
Liver	M4 M6	M2 M31 M33 M34 M35

Crop Field Trials and Residue Decline—Wheat

Canadian Trials:
Twenty field trials were conducted throughout Canada on wheat in during the 2003 growing season. At each test location in Canada, wheat was treated with a single postemergent application with one of the three following formulations at a target seasonal rate of 70 g a.i./ha: 100EC Lead Variant (formulation A-12303C), 100EC Alternate Variant (formulation A-12303D) or 120EC Aromatic 200 (formulation A-12413B). The applications were made up to the fourth tiller on wheat, corresponding to the 3- to 6-leaf growth stage (BBCH 23). All formulations contained cloquintocet-mexyl (CGA 185072) as a safener. One of the following adjuvants was added to the spray mixture at a rate of 0.7 L/ha: Merge, A12727M or A12727S. All wheat samples were collected at normal maturity: 4–25 days following application for forage, 28–50 days following application for hay (hay was left to dry for 2–26 days), 58–98 days following application for straw and grain.

American Trials:
Twenty-one field trials were conducted throughout the United States on wheat during the 2003 growing season. At each test location in the United States, wheat was treated with a single post foliar broadcast application of either NOA 407855 100EC or NOA 407855 120EC (containing respectively 100 g or 120 g of pinoxaden/L) at a target seasonal rate of 72.5 g a.i./ha. The safener cloquintocet-mexyl (CGA 185072) was included in the formulation at a ratio of 4:1. The adjuvant Merge (0.25% v/v) and a crop oil concentrate (2% v/v) were added to the spray mixture for all applications. Wheat forage and hay were harvested at a PHI of 30 days, and wheat straw and grain at a PHI of 60 days.

Commodity	Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	SD
Combined Residues of Pinoxaden, M2, M4 and M6									
Wheat spring forage (United States)	72.5	10	6	0.96	3.58	2.84	1.16	1.66	1.03
		20	6	0.14	0.85	0.83	0.68	0.56	0.33
		30	42	0.06	0.95	0.94	0.14	0.24	0.22
		40	6	0.07	0.20	0.18	0.08	0.11	0.06
Wheat fall forage (United States)	72.5	10	2	2.53	3.46	3.00	—	3	—
		20	4	0.90	2.34	2.24	1.54	1.58	0.77
		30	20	0.06	3.07	2.99	1.54	1.41	0.82
		40	4	0.06	1.40	1.35	0.83	0.78	0.67
Wheat hay (United States)	72.5	10	4	2.24	3.56	3.33	2.86	2.88	0.58
		20	6	0.14	2.64	2.44	1.65	1.43	1.06
		30	42	0.06	1.71	1.31	0.28	0.49	0.43
		40	6	0.09	0.51	0.47	0.15	0.24	0.18
Wheat straw (United States)	72.5	46	4	0.27	0.58	0.54	0.49	0.46	0.13
		53	4	0.22	0.62	0.62	0.53	0.48	0.19
		60	42	0.09	1.49	1.23	0.34	0.43	0.32
		67	4	0.14	0.59	0.58	0.37	0.37	0.24
	217.5	60	2	0.19	0.20	0.20	—	0.20	—
	362.5	60	2	0.91	0.98	0.95	—	0.95	—
Wheat grain (United States)	72.5	46	4	0.14	0.77	0.52	0.24	0.35	0.30
		53	4	0.23	0.53	0.38	0.36	0.37	0.13
		60	42	0.05	0.72	0.61	0.18	0.22	0.15
		67	4	0.45	0.65	0.55	0.49	0.52	0.09
	217.5	60	2	0.07	0.08	0.08	—	0.08	—
	362.5	60	2	0.60	0.66	0.63	—	0.63	—
Wheat forage (Canada)	70	4–5	12	1.57	3.02	2.86	2.28	2.25	0.48
		6–8	31	0.66	3.75	3.21	1.50	1.53	0.60
		10–17	7	0.13	0.54	0.39	0.24	0.25	0.14
		22–25	6	0.06	0.27	0.27	0.08	0.11	0.08
		29–31	2	0.06	0.14	0.14	0.10	0.10	—

Wheat hay (Canada)	70.0	22	1	0.87		0.87	—	—	—
		28–36	34	0.06	0.92	0.78	0.12	0.17	0.18
		37–49	20	0.06	0.14	0.14	0.09	0.09	0.02
		50	5	0.06	0.08	—	0.06	0.06	0.01
		57	1	0.06	—	—	—	—	—
		64	1	0.06	—	—	—	—	—
Wheat straw (Canada)	70.0	58–72	37	0.06	0.19	0.19	0.07	0.08	0.03
		74–79	9	0.06	0.09	0.09	0.06	0.07	0.01
		80–88	6	0.06	0.09	0.09	0.06	0.07	0.01
		90–101	8	0.06	0.06	0.06	0.06	0.06	0
Wheat grain (Canada)	70	58–72	37	0.03	0.08	0.08	0.03	0.03	0.01
		74–79	9	0.03	0.03	0.03	0.03	0.03	0
		80–88	6	0.03	0.04	0.03	0.03	0.03	0
		90–101	8	0.03	0.03	0.03	0.03	0.03	0
		58–101	60	<0.01	<0.01	<0.01	<0.01	<0.01	0

Crop Field Trials and Residue Decline—Barley

Canadian Trials:
Sixteen field trials were conducted throughout Canada on barley during the 2003 growing season. At each test location in Canada, barley was treated with a single postemergent application with one of the three following formulations at a target seasonal rate of 70 g a.i./ha: 100EC Lead Variant (formulation A-12303C), 100EC Alternate Variant (formulation A-12303D) or 120EC Aromatic 200 (formulation A-12413B). The applications were made up to the fourth tiller on barley, corresponding to the 3- to 6-leaf growth stage (BBCH 23). All formulations contained cloquintocet-mexyl (CGA 185072) as a safener. One of the following adjuvants was added to the spray mixture at a rate of 0.7 L/ha: Merge, A12727M or A12727S. All barley samples were collected at normal maturity: 26–48 days following application for hay (hay was left to dry for 0–9 days), 54–89 days following application for straw and grain.

American Trials:
Twelve field trials were conducted throughout the United States on barley during the 2003 growing season. At each test location in the United States, barley was treated with a single postemergent foliar broadcast application of either NOA 407855 100EC or NOA 407855 120EC (containing respectively 100 g or 120 g of pinoxaden/L) at a target seasonal rate of 72.5 g a.i./ha. The safener cloquintocet-mexyl (CGA 185072) was included in the formulation at a ratio of 4:1. The adjuvant Merge (0.25% v/v) and a crop oil concentrate (2% v/v) were added to the spray mixture for all applications. Barley hay was harvested at a PHI) of 30 days and barley straw and grain at a PHI of 60 days.

Commodity	**Rate (g a.i./ha)**	**PHI (days)**	**Residue Levels (ppm)**						
			n	**Min.**	**Max.**	**HAFT**	**Median**	**Mean**	**SD**
Combined Residues of pinoxaden, M2, M4 and M6									
Barley hay (United States)	72.5	10	4	1.50	2.83	2.69	2.22	2.19	0.61
		20	4	0.17	0.23	0.22	0.19	0.20	0.02
		30	24	0.06	1.10	0.71	0.09	0.18	0.22
		40	4	0.06	0.14	0.14	0.10	0.10	0.04
Barley straw (United States)	72.5	46	4	0.24	0.48	0.43	0.37	0.36	0.10
		53	4	0.26	0.65	0.46	0.41	0.43	0.16
		60	24	0.09	0.62	0.52	0.25	0.29	0.16
		67	4	0.22	0.36	0.31	0.31	0.30	0.06

Barley grain (United States)	72.5	46	4	0.24	0.40	0.38	0.33	0.33	0.07
		53	4	0.32	0.64	0.48	0.47	0.48	0.13
		60	24	0.09	0.69	0.66	0.23	0.27	0.18
		67	4	0.16	0.51	0.40	0.34	0.34	0.15
Barley hay (Canada)	70.0	15	1	0.589		0.589	—	—	—
		22	2	0.13	0.17	0.17	0.15	0.15	—
		26–36	30	0.06	0.77	0.74	0.17	0.24	0.2
		42–49	23	0.06	0.12	0.12	0.08	0.08	0.02
Barley straw (Canada)	70	46	1	0.06		0.06	—	—	—
		54–70	29	0.06	0.22	0.18	0.08	0.10	0.05
		73–89	22	0.06	0.13	0.12	0.06	0.07	0.02
Barley grain (Canada)	70.0	46	1	0.03		0.03	—	—	—
		54–70	29	0.03	0.16	0.15	0.06	0.07	0.04
		73–89	22	0.03	0.07	0.07	0.04	0.04	0.01

Proposed Maximum Residue Limits

Wheat grain	1.3 ppm*
Wheat bran	3.0 ppm*
Barley grain	0.9 ppm*
Barley bran	1.6 ppm*
Milk	0.02 ppm**
Fat, meat and meat by-products of cattle, goats, hogs, horses and sheep	0.04 ppm**
Fat, meat and meat by-products of poultry	0.06 ppm*
Eggs	0.06 ppm*

* Combined residues of pinoxaden (as M2), M2, M4 (free and conjugate) and M6.

** Combined residues of pinoxaden (as M2), M2 and M4 (free and conjugate).

Processing Studies—Wheat

The processing study was conducted with wheat plants treated at 70 g a.i./ha (1.2× GAP) and 365 g a.i./ha (6× GAP).

Raw Agricultural Commodity	Processed Commodity	Total Rate (g a.i./ha)	PHI (days)	Combined Residues (M2 + M4 + M6) (ppm)	Processing Factor	Mean Processing Factor
Wheat grain	Grain	70	60	0.449		0.2× for aspirated grain fraction 0.2× for flour 0.7× for middling 1× for shorts 0.7× for germ (Due to the difference between the two values in wheat bran, the concentration factors were not averaged.)
	Aspirated grain fraction			0.068	0.15×	
	Bran			0.63	1.4×	
	Flour			0.089	0.2×	
	Middling			0.26	0.6×	
	Shorts			0.432	1×	
	Germ			0.273	0.6×	
Wheat grain	Grain	365	60	1.26		
	Aspirated grain fraction			0.257	0.2×	
	Bran			5.81	4.6×	
	Flour			0.212	0.17×	
	Middling			0.875	0.7×	
	Shorts			1.26	1×	
	Germ			0.96	0.8×	

Processing Studies —Barley

The processing study was conducted with barley plants treated at 70 g a.i./ha (1.2× GAP) and 365 g a.i./ha (6× GAP).

Raw Agricultural Commodity	Processed Commodity	Total Rate (g a.i./ha)	PHI (days)	Combined Residues (M2 + M4 + M6) (ppm)	Processing Factor	Mean Processing Factor
Barley grain	Grain	70	60	0.28		0.42× for flour 0.99× for pearled barley (Due to the difference between the two values in barley bran, the concentration factors were not averaged.)
	Flour			0.12	0.43×	
	Bran			0.68	2.43×	
	Pearled barley			0.32	1.14×	
	Grain	365	60	1.66		
	Flour			0.67	0.40×	
	Bran			1.36	0.82×	
	Pearled barley			1.4	0.84×	

Livestock Feeding

Dairy Cow
The metabolite M4 was administered once daily in a gelatin capsule via a balling gun to nine Holstein dairy cattle for 29 to 30 consecutive days. Cows were administered daily doses of either 21.05, 63.15 or 210.52 mg a.i./day, corresponding to 1 ppm, 3 ppm or 10 ppm of M4 in their diet. Milk was collected twice daily and composite samples were prepared from AM and PM milk samples for each cow on days 0, 2, 5, 8, 12, 15, 19, 22 and 28. Blood and tissue samples were collected at sacrifice. Tissue and milk samples were analyzed for residues of M4 and M6.

There were no quantifiable residues (<0.01 ppm; LOQ) of M4 or M6 in milk collected from animals treated at the highest dose, nor were there any quantifiable residues (<0.02 ppm; LOQ) of either metabolite detected in any of the tissues samples. As residue levels in samples taken from animals at the highest treatment dose were all below the LOQ, no additional analysis of samples from the two lower treatment dose groups was done.

Laying Hen
The metabolite M4 was administered *ad libitum* to White Leghorn hens in treated feed for 28 consecutive days. Hens were administered doses equivalent to 0.040, 0.120 and 0.372 mg a.i./kg bw/day, corresponding to levels of 0.5, 1.5 and 5.0 ppm in their diet. Each treatment group consisted of 15 hens and all tissue and egg samples were pooled within subgroups (n=5), yielding three samples per treatment group. Whole eggs were collected on days 0, 1, 3, 6, 9, 13, 16, 20, 23 and 28, and pooled within treatment groups.

There were no quantifiable residues (<0.02 ppm; LOQ) of M4 or M6 in eggs collected from animals treated at the highest dose, nor were there any quantifiable residues (<0.02 ppm; LOQs) of either metabolite detected in any of the tissue samples from the same treatment group. As residue levels in samples taken from animals at the highest treatment dose were all below the LOQ, no additional analysis of samples from the two lower treatment groups was done.

Storage Stability

Animal Matrices
The freezer storage stability data indicated that residues of M4 and M6 were stable when stored frozen at -20°C for up to 3 months in muscle, liver, milk and eggs.

Only freezer storage stability of the metabolites M4 and M6 in livestock matrices was demonstrated. According to the wheat metabolism studies, pinoxaden was completely and rapidly converted to M2 and subsequently M4 (predominant metabolite) in livestock feed items. Therefore, the transfer of measurable residues (>LOQ) of pinoxaden and the metabolite M2 (components of the ROC) to meat, milk and eggs is not expected, as supported by the livestock metabolism studies. As such, the freezer storage stability of pinoxaden and M2 in livestock matrices is not required for the purposes of this submission.

Plant Matrices
The freezer storage stability data indicated that residues of M2, M4, M6 and M10 were stable at ≤-18°C for 15 months in wheat whole plant, straw and grain.

Processed Commodities
Wheat: The wheat processed fractions were stored frozen for a maximum of 5.7 months prior to analysis. **The freezer storage stability of the metabolites M2, M4 and M6 was not demonstrated in wheat processed fractions (aspirated grain fraction, bran, flour, middling, shorts and germ).**

Barley: The barley processed fractions were stored frozen for a maximum of 13.9 months prior to analysis. **The storage stability of the metabolites M2, M4 and M6 was not demonstrated in barley processed fractions (bran, flour and pearled barley).**

REQUIRED DATA: Freezer storage stability data demonstrating the stability of the metabolites M2, M4 and M6 residues in cereal processed fractions must be submitted to validate the frozen storage intervals of the processed samples in the two following processing studies: Study Nos 824-02 (wheat) and 825-02 (barley).

Appendix III Environmental Assessment

Table 1 Technical Product: Pinoxaden

Property	Result	Comment
Colour and physical state	Light beige	
Odour	Sweet odour	
Melting point or range	120.5–121.6°C	
Density	1.16×10^3 kg/m^3 at 24°C	
Vapour pressure	2.0×10^{-7} Pa at 20°C 4.6×10^{-7} Pa at 25°C	Relatively non-volatile under field conditions (Kennedy and Talbert 1977)
Henry's law constant at 20°C	9.09×10^{-12} atm m^3/mole $1/H = 1.1 \times 10^6$	Low potential for volatilization from water and moist surfaces (USEPA 1995)
Ultraviolet (UV) – visible spectrum	**Conditions** λ_{max} Neutral solution 210, 258 Acidic solution 210, 254 Basic solution 220, 252 No absorption maximum between 350 and 750 was observed in any of the three solutions.	Low potential for phototransformation
Solubility in water at 25°C	200 mg/L	Determined at a low pH. Very soluble (Cohen et al. 1984)
Solubility in organic solvents at 25°C	**Solvent** **Solubility (g/L)** Acetone 250 Dichloromethane >500 Ethyl acetate 130 Hexane 1.0 Methanol 260 Octanol 140 Toluene 130	
n-Octanol–water partition coefficient (K_{ow}) at 25°C	$\log K_{ow} = 3.2$	Potential bioaccumulation in biota

Property	Result	Comment
Dissociation constant (pK_a)	None, no dissociable moiety.	
Stability (temperature, metal)	The product is chemically stable in the presence of iron, aluminum and their ions for at least 14 days. Stable when stored for 14 days at 54°C.	

Table 2 Physico-Chemical Properties of M2

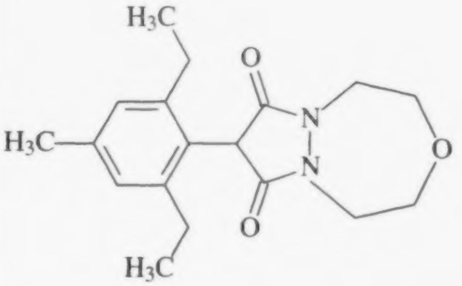
Parameter	Value	Comment
Chemical structure		
IUPAC name	8-(2,6-diethyl-4-methyl-pheny-l)-tetrahydro-pyraxolo[1,2-d][1,4,5] oxadiazepine-7,9-dione	
Empirical formula	$C_{18}H_{24}N_2O_3$	
Molecular mass	316.4 g/mole	

Table 3 Physico-Chemical Properties of M3

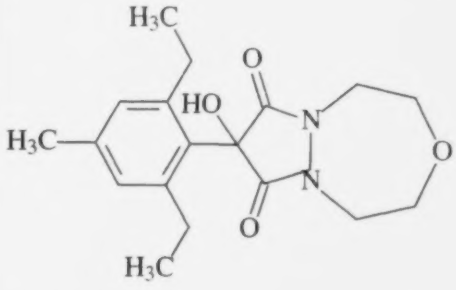
Parameter	Value	Comment
Chemical structure		
IUPAC name	8-(2,6-Diethyl-4-methyl-phenyl)-8-hydroxytetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepine-7,9-dione	
Empirical formula	$C_{18}H_{24}N_2O_4$	
Molecular mass	332.4 g/mole	

Table 4 End-use Product and Adjuvant: AXIAL 100EC Herbicide and ADIGOR Adjuvant (A12127S Formulation)

Property	AXIAL 100EC Herbicide	ADIGOR Adjuvant (A12127S Formulation)
Colour	Yellow orange	Not provided
Odour	Thymol like odour	Aromatic odour
Physical state	Liquid	Liquid
Formulation type	Emulsifiable concentrate	Emulsifiable concentrate
Nominal guarantee	Pinoxaden: 100 g/L	Rape see oil methyl ester: 48.8% Ethoxylated alcohols, C16-18 and C18 unsaturated: 28.2%

Property	AXIAL 100EC Herbicide	ADIGOR Adjuvant (A12127S Formulation)
Formulants	The product does not contain any USEPA or PMRA List 1 formulants or formulants known to be TSMP Track 1 substances. It contains 55.65% Naphthalene Depleted Aromatic 200, a USEPA and PMRA List 2 formulant.	The product does not contain any USEPA or PMRA List 1 formulants or formulants known to be TSMP Track 1 substances. It contains 23% Solvesso 200 ND, a USEPA and PMRA List 2 formulant.
Container material and description	1 L, 5 L, 10 L, 15 L, 15 L, 55 L, 115 L, 200 L, and bulk fluorinated HDPE containers	5.7 L, 11.4 L, 200 L and bulk fluorinated HDPE containers
Density or specific gravity	1.03 g/cm^3 at 20°C	0.922
pH of 1% dispersion in water	5.3 (1% dispersion in water at 25°C)	Expected to be neutral
Oxidizing or reducing action	These products do not contain any oxidizing or reducing agents.	
Storage stability	Data showed that the product is stable when stored for 2 weeks at 54°C in a hermetically closed glass bottle and for one year at 20°C in fluorinated HDPE packaging.	Expected to be stable
Explodability	No explosive materials present in the products.	

Table 5 Fate and Behaviour in the Terrestrial Environment

Property	Test Substance	Additional Information	Value	Interpretation
Abiotic Transformation				
Hydrolysis	Pinoxaden	(25°C) pH 4 pH 5 pH 7 pH 9 (15°C) pH 7 pH 9	$t_{1/2}$ = 18.1 days $t_{1/2}$ = 17.5 days $t_{1/2}$ = 9.9 days $t_{1/2}$ = 0.2 days $t_{1/2}$ = 23.7 days $t_{1/2}$ = 0.7 days	Hydrolysis is expected to be an important route of transformation at higher pH levels.
	M2 (NOA 407854)		Stable	Hydrolysis is not a route of transformation.
	M3 (NOA 447204)	pH 5 pH 7 pH 9	Stable $t_{1/2}$ = 57 days $t_{1/2}$ = 0.6 days	Hydrolysis is expected to be an important route of transformation at higher pH levels.
Phototransformation on soil	Pinoxaden		The dark half-life (4.97–6.6 days) was shorter than the irradiated half-life (9.9–10.5 days).	Phototransformation is not an important route of transformation.
	M2		$t_{1/2}$ = 19.8 day	Route of transformation.
	M3			No data was available to determine if this is a route of transformation.
Biotransformation				
Biotransformation in aerobic soil	Pinoxaden	Phenyl Oxadiazepin Pyrazolo	DT_{50} = 0.2 day DT_{50} = 0.2 day DT_{50} = 0.3 day	Non-persistant (Goring et al. 1975)
	M2	Phenyl Oxadiazepin Pyrazolo	DT_{50} = 7.1 day DT_{50} = 4.2 day DT_{50} = 3.8 day	Non-persistant (Goring et al. 1975)
	M3	Phenyl Oxadiazepin Pyrazolo	$t_{1/2}$ = 48 day $t_{1/2}$ = 96 day $t_{1/2}$ = 58 day	Slight to moderately persistant (Goring et al. 1975)
	ADIGOR Adjuvant (A12127S formulation)	Oleic acid Methyl ester	DT_{50} = 7 days	Non-persistant (Goring et al. 1975)

Property	Test Substance	Additional Information	Value	Interpretation
Mobility				
Adsorption or desorption in soil	Pinoxaden	Loamy sand $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	4.903 403 7.001 479	Moderate mobility (McCall et al. 1981)
		Loam $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	13.097 453 19.263 523	Low to moderate mobility (McCall et al. 1981)
		Sand $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	1.041 299 2.427 595	Moderate to high mobility (McCall et al. 1981)
		Loamy sand $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	10.954 337 16.648 516	Low to moderate mobility (McCall et al. 1981)
		Silty clay loam $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	8.897 852 10.232 946	Low to moderate mobility (McCall et al. 1981)
	M2	Loamy sand $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	0.064 5.2 110 2.699	Very high mobility (McCall et al. 1981)
		Loam $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	0.178 6.0 1.083 19	Very high mobility (McCall et al. 1981)
		Sand $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	0.080 23 5.652 151	Very high mobility (McCall et al. 1981)

Property	Test Substance	Additional Information	Value	Interpretation
		Loam $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	0.136 4.2 1.301 16	Very high mobility (McCall et al. 1981)
		Silty clay loam $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	0.277 27 18.383 173	Very high mobility (McCall et al. 1981)
	M3	Loamy sand $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	0.280 23 0.741 47	Very high mobility (McCall et al. 1981)
		Loam $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	0.764 26 1.385 45	Very high mobility (McCall et al. 1981)
		Sand $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	0.121 35 0.271 71	Very high mobility (McCall et al. 1981)
		Loam $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	0.856 26 1.813 58	Very high mobility (McCall et al. 1981)
		Silty clay loam $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$ $K_{d\text{-}des}$ $K_{oc\text{-}des}$	0.500 48 1.462 120	Very high mobility (McCall et al. 1981)
Soil leaching	Oleic acid methyl ester	16-18C: 12-15C: 7-10C: 3-8C: C = carbon chain length	15 cm 25–30 cm 40–50 cm 60 cm	Transformation products of biotransformation of oleic acid methyl ester (component of ADIGOR Adjuvant[1]) may leach to depth

Property	Test Substance	Additional Information	Value	Interpretation
Field studies				
Field dissipation	Pinoxaden	Manitoba	DT$_{50}$ 2 day DT$_{90}$ 7 day	Pinoxaden is not expected to persist under field conditions.
		Saskatchewan	DT$_{50}$ 5 day DT$_{90}$ 18 day	
		Alberta	DT$_{50}$ 2 day DT$_{90}$ 6 day	
		North Dakota	DT$_{50}$ 3 day DT$_{90}$ 11 day	
	M2	Manitoba	DT$_{50}$ 2 day DT$_{90}$ 8 day	M2 is not expected to persist under field conditions.
		Saskatchewan	DT$_{50}$ 16 day DT$_{90}$ 53 day	
		Alberta	DT$_{50}$ 15 day DT$_{90}$ 50.5 day	
		North Dakota	DT$_{50}$ 5 day DT$_{90}$ 16 day	
	M3	Manitoba	DT$_{50}$ 315 day DT$_{90}$ 1047 day	M3 is expected to persist under field conditions.
		Saskatchewan	DT$_{50}$ 178 day DT$_{90}$ 590.5 day	
		Alberta	Could not calculate	
		North Dakota	DT$_{50}$ 161 day DT$_{90}$ 536 day	

Table 6 Fate and Behaviour in the Aquatic Environment

Property	Test Material	Additional Information	Value	Comments
Abiotic Transformation				
Hydrolysis	Pinoxaden	(25°C) pH 4	$t_{1/2}$ = 18.1 day	Hydrolysis is expected to be an important route of transformation at higher pHs.
		pH 5	$t_{1/2}$ = 17.5 day	
		pH 7	$t_{1/2}$ = 9.9 day	
		pH 9	$t_{1/2}$ = 0.2 day	
		(15°C) pH 7	$t_{1/2}$ = 23.7 day	
		pH 9	$t_{1/2}$ = 0.7 day	
	M2		Stable	Hydrolysis is not a route of transformation.
	M3	pH 5	Stable	Hydrolysis is expected to be an important route of transformation at higher pHs.
		pH 7	$t_{1/2}$ = 57 day	
		pH 9	$t_{1/2}$ = 15 hour	

Property	Test Material	Additional Information	Value	Comments
Phototransformation in water	Pinoxaden	30–50°N 60°N	$t_{½}$ = 14 day $t_{½}$ = 20.6 day	Potential route of transformation.
Biotransformation				
Biotransformation in aerobic water systems	Pinoxaden	Water Entire system	$DT_{50} < 1$ day $DT_{50} < 1$ day	Non-persistant (McEwen and Stephenson 1979)
	M2	Water Entire system	$t_{½}$ = 14 day n/a	Non-persistant (McEwen and Stephenson 1979)
	ADIGOR Adjuvant (A12127S formulation)	Entire system	DT_{50} = 7 days	Non-persistant (McEwen and Stephenson 1979)
Biotransformation in anaerobic water systems	Pinoxaden	Water Entire system	$DT_{50} < 1$ day	Non-persistant (McEwen and Stephenson 1979)
	M2	Water Entire system	$t_{½}$ = 14–21 day n/a	Non-persistant to slightly persistant (McEwen and Stephenson 1979)

Table 7 Transformation Products in Terrestrial Environments

Fate Process	Test Material	Major Transformation Products	Minor Transformation Products
Hydrolysis	Pinoxaden	M2 (NOA 407854)	None reported
Phototransformation on soil	Pinoxaden	M2 (NOA 407854), M3 (NOA 447204)	NOA 437397
Biotransformation in aerobic soil	Pinoxaden	M2 (NOA 407854), M3 (NOA 447204)	Not identified
Biotransformation in anaerobic soil (flooded soil)	n/a	n/a	n/a
Field dissipation	AXIAL 120EC Herbicide	M2 (NOA 407854), M3 (NOA 447204)	None sampled for

Table 8 Transformation Products in Aquatic Environments

Fate Process	Test Material	Major Transformation Products	Minor Transformation Products
Hydrolysis	Pinoxaden	M2 (NOA 407854)	None reported
Phototransformation on water	Pinoxaden	M2 (NOA 407854)	None reported
Biotransformation in aerobic aquatic system	Pinoxaden	M2 (NOA 407854)	M3 (NOA 447204)
Biotransformation in anaerobic aquatic system	Pinoxaden	M2 (NOA 407854)[1]	M3 (NOA 447204)[1]

[1] Studies conducted in the European Union and the United States.

Table 9 Major Groundwater and Surface Water Model Inputs for Level 1 Assessment of Pinoxaden and Transformation Products

Type of Input	Parameter	Value
Application Information	Crop(s) to be treated	Spring wheat, durum wheat, barley
	Maximum allowable application rate per year (kg a.i./ha)	0.06
	Maximum rate each application (kg a.i./ha)	0.06
	Maximum number of applications per year	1
	Minimum interval between applications (days)	n/a
	Method of application	Groundboom sprayer
Environmental Fate Characteristics **Pinoxaden**	Hydrolysis half-life at pH 7 (days)	24
	Photolysis half-life in water (days)	21
	Adsorption K_{oc} (mL/g)	299
	Aerobic soil biotransformation half-life (days)	0.3
	Aerobic aquatic biotransformation half-life (days)	1
	Anaerobic aquatic biotransformation half-life (days)	1
Environmental Fate Characteristics **Transformation product M2**	Hydrolysis half-life at pH 7 (days)	Stable
	Photolysis half-life in water (days)	10.1
	Adsorption K_{oc} (mL/g)	4.2
	Aerobic soil biotransformation half-life (days)	4.8*
	Aerobic aquatic biotransformation half-life (days)	13.8
	Anaerobic aquatic biotransformation half-life (days)	20.6

Type of Input	Parameter	Value
Environmental Fate Characteristics **Transformation product M3**	Hydrolysis half-life at pH 7 (days)	57
	Photolysis half-life in water (days)	Not available; assume stable
	Adsorption K_{oc} (mL/g)	23
	Aerobic soil biotransformation half-life (days)	96
	Aerobic aquatic biotransformation half-life (days)	Not available; assume stable
	Anaerobic aquatic biotransformation half-life (days)	96*

* Longest half-life values were used for modelling rather than DT_{50}.

Table 10 Level 1 Estimated Environmental Concentrations of Pinoxaden and Transformation Products in Potential Drinking Water Sources

Compound	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)			
			Reservoir		Dugout	
	Acute[1]	Chronic[2]	Acute[3]	Chronic[4]	Acute[3]	Chronic[4]
Pinoxaden	0	0	0.24	0.002	0.07	0.0008
M2 (NOA 407854)	1.14	0.95	1.99	0.2	0.97	0.1
M3 (NOA 447204)	0.18	0.13	2.2	0.34	2	0.43

[1] 90th percentile of daily average concentrations

[2] 90th percentile of yearly average concentrations

[3] 90th percentile of yearly peak concentrations

[4] 90th percentile of yearly average concentrations

Table 11 Maximum Pinoxaden EEC in Vegetation and Insects after a Direct Overspray

Matrix	EEC (mg a.i./kg fw)[a]	Fresh to Dry Weight Ratios	EEC (mg a.i./kg dw)
Short range grass	13	3.3[b]	42
Leaves and leafy crops	7	11[b]	74
Long grass	6	4.4[b]	26
Forage crops	7	5.4[b]	39
Small insects	3	3.8[c]	12
Pods with seeds	1	3.9[c]	3
Large insects	1	3.8[c]	2
Grain and seeds	1	3.8[c]	2
Fruit	0.8	7.6[c]	6

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)

[b] Fresh to dry weight ratios from Harris (1975)

[c] Fresh to dry weight ratios from Spector (1956)

Table 12 Maximum AXIAL 100EC Herbicide EEC in Vegetation and Insects after a Direct Overspray

Matrix	EEC (mg EP/kg fw)[a]	Fresh to Dry Weight Ratios	EEC (mg EP/kg dw)
Short range grass	132	3.3[b]	436
Leaves and leafy crops	70	11[b]	761
Long grass	61	4.4[b]	266
Forage crops	74	5.4[b]	401
Small insects	32	3.8[c]	122
Pods with seeds	7	3.9[c]	26
Large insects	6	3.8[c]	21
Grain and seeds	6	3.8[c]	21
Fruit	8.0	7.6[c]	63

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)

[b] Fresh to dry weight ratios from Harris (1975)

[c] Fresh to dry weight ratios from Spector (1956)

Table 13 Maximum ADIGOR Adjuvant (A12127S Formulation) EEC in Vegetation and Insects after a Direct Overspray

Matrix	EEC (mg a.i./kg fw)[a]	Fresh to Dry Weight Ratios	EEC (mg a.i./kg dw)
Short range grass	138	3.3[b]	456
Leaves and leafy crops	72	11[b]	795
Long grass	63	4.4[b]	278
Forage crops	77	5.4[b]	418
Small insects	34	3.8[c]	128
Pods with seeds	7	3.9[c]	27
Large insects	6	3.8[c]	22
Grain and seeds	6	3.8[c]	22
Fruit	8.6	7.6[c]	65.7

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)

[b] Fresh to dry weight ratios from Harris (1975)

[c] Fresh to dry weight ratios from Spector (1956)

Table 14 Maximum Pinoxaden EEC in Diets of Birds and Mammals

Organism	Matrix	EEC (mg a.i./kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	10.5
Mallard duck	30% large insects 70% grain	2.03
Rat	70% short grass 20% grain/seeds 10% large insects	30.27
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	30.09
Rabbit	25% short grass 25% leaves and leafy crops 25% long grass 25% forage crops	45.26

Table 15 Maximum AXIAL 100EC Herbicide EEC in Diets of Birds and Mammals

Organism	Matrix	EEC (mg EP/kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	108.2
Mallard duck	30% large insects 70% grain	20.9
Rat	70% short grass 20% grain/seeds 10% large insects	311.8
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	309.9
Rabbit	25% short grass 25% leaves and leafy crops 25% long grass 25% forage crops	466.2

Table 16 Maximum ADIGOR Adjuvant (A12127S formulation) EEC in Diets of Birds and Mammals

Organism	Matrix	EEC (mg a.i./kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	113
Mallard duck	30% large insects 70% grain	21.83
Rat	70% short grass 20% grain/seeds 10% large insects	325.6
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	323.64
Rabbit	25% short grass 25% leaves and leafy crops 25% long grass 25% forage crops	486.86

Table 17 Effects on Terrestrial Organisms

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Invertebrates				
Earthworm	14-day Acute (artificial soil)	Pinoxaden (97%)	$LC_{50} > 1000$ mg a.i./kg NOEC = 178 mg a.i./kg	
		M2 (99.6%)	$LC_{50} > 1000$ mg/kg NOEC = 556 mg/kg	
		M3 (97%)	$LC_{50} > 1000$ mg/kg NOEC = 178 mg/kg	
Bee	Oral	Pinoxaden	Data gap	Unknown
		AXIAL 100EC	$LC_{50} = 93.0$ µg EP/bee NOEC = 9.3 µg EP/bee	Practically non-toxic
		A12127R	$LC_{50} > 200$ µg/bee NOEC <12.5 µg/bee	Practically non-toxic
	48-hour Contact	Pinoxaden (98.3 %)	$LD_{50} > 100$ µg a.i./bee NOEL = 6.3 µg a.i./bee	Practically non-toxic
		AXIAL 100EC	$LD_{50} = 84.0$ µg EP/bee NOEC = 8.4 µg EP/bee	Practically non-toxic
		A12127R	$LC_{50} > 200$ µg/bee NOEC < 12.5 µg/bee	Practically non-toxic
Predatory arthropod	Contact	Waiver accepted based on bee contact results.		
Parasitic arthropod	Contact	Waiver accepted based on bee contact results.		
Birds				
Bobwhite quail	14-day Acute	Pinoxaden (98.5%)	$LD_{50} > 2250$ mg a.i./kg bw NOEL = 810 mg a.i./kg bw	Practically non-toxic
	8-day Dietary	Pinoxaden	$LC_{50} > 5970$ mg a.i./kg dw NOEC = 5970 mg a.i./kg dw	
	22-week Reproduction	M2 (NOA 407854)	NOEC 107 mg/kg dw	
Mallard duck	8-day Dietary	Pinoxaden	$LC_{50} > 5970$ mg a.i./kg dw NOEC 3220 mg a.i./kg dw	Practically non-toxic
	22-week Reproduction	M2 (NOA 407854)	NOEC = 1050 mg/kg dw	

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Mammals				
Rat	14-day Acute	Pinoxaden	$LD_{50} > 5000$ mg a.i./kg bw	Low toxicity
		M3 (NOA 447204)	$LD_{50} = 1098$ mg/kg bw	Slightly toxic
		AXIAL 100EC	$LD_{50} = 3129$ mg/kg bw	Low toxicity
	13-week Dietary	Pinoxaden	NOAEL = 5000 ppm (466/527 mg/kg bw/d m/f) LOAEL = 10000 ppm (900/962 mg/kg bw/d m/f)	
		M3 (NOA 447204)	NOAEL = 1000 ppm LOAEL = 6000 ppm	
	120-day Reproduction	Pinoxaden	Parental and Offspring NOAEL = 250 mg/kg bw/d LOAEL = 500 mg/kg bw/d Reproduction NOAEL = 500 mg/kg bw/d LOAEL not observed	
	15-day Developmental	Pinoxaden	NOAEL = 30 mg/kg bw/d LOAEL = 300 mg/kg bw/d	
Mouse	13-week Dietary	Pinoxaden	NOAEL = 2500 ppm m (365 mg/kg bw/d m)	
Vascular Plants				
Vascular plant	14-day Seedling emergence	AXIAL 100EC (10.1% Pinoxaden)	$EC_{25} = 207.9$ g EP/ha (ryegrass) $EC_{25} = 1480.2$ g EP/ha (lettuce)	
		A12127R	$EC_{50} > 4.0$ kg/ha	
	14-day Vegetative vigour	AXIAL 100EC (10.1% Pinoxaden)	$EC_{25} = 53.8$ g EP/ha (oat) $EC_{25} = 990.1$ g EP/ha (cabbage)	

[a] Atkins et al. (1981) for bees and the USEPA classification for others, where applicable.

Table 18 Effects on Aquatic Organisms

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Freshwater species				
Daphnia magna	Acute (48-hours)	Pinoxaden	Data gap	Unknown
		M2	$EC_{50} > 99.0$ NOEC = 99.0 mg/L	Practically non-toxic
		M3	$EC_{50} > 120$ mg/L NOEC = 56 mg/L	Practically non-toxic
		AXIAL 100EC	Data gap	Unknown
		A12127R	$EC_{50} = 7.1$ mg/L NOEC = 0.31 mg/L	Moderately toxic
	Chronic (21-days)	M2 (reproduction)	NOEC = 5.87 mg/L	
Rainbow trout	Acute (96-hours)	Pinoxaden	Currently not received	Unknown
		M2	$LC_{50} > 105$ mg/L NOEL = 105 mg/L	Practically non-toxic
		M3	$LC_{50} > 120$ mg/L NOEL = 16 mg/L	Practically non-toxic
		AXIAL 100EC	Not received	Unknown
		A12127R	$LC_{50} = 9.6$ mg/L NOEC = 2.2 mg/L	Moderately toxic
	Chronic	Pinoxaden	Data gap	Unknown
Bluegill sunfish	The fathead minnow study submitted was accepted in lieu of the bluegill study based on the Joint Review status of this submission and the USEPA acceptance of a fathead minnow or bluegill study for a warm water fish requirement.			
Fathead minnow	Acute (96-hours)	Pinoxaden	$LC_{50} = 20$ mg a.i./L NOEL = 16 mg a.i./L	Slightly toxic
	Chronic	Pinoxaden	Data gap	
		M2 (NOA 407854)	Currently not received	
Freshwater algae	Acute—Blue-green (96-hours)	Pinoxaden	$IC_{50} = 3.3$ mg a.i./L NOEC = 0.13 mg a.i./L	
	Acute—Green (96-hours)	Pinoxaden	Currently not received	
		M2	Currently not received	
		M3	Currently not received	
		AXIAL 100EC	$IC_{50} = 0.427$ mg EP/L NOEC = 0.0427 mg EP/L	
		A12127R	$EC_{50} = 0.64$ mg/L NOEC = 0.2 mg/L	

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
	Acute—Diatom (96-hours)	Pinoxaden	Currently not received	
Vascular plant	Dissolved (7-days)	Pinoxaden	Data gap	Unknown
		M2	Currently not received	Unknown
		M3	Currently not received	Unknown
		AXIAL 100EC	Currently not received	Unknown
		A12127R	EC_{50} >100 mg/L NOEC = 1/10 EC_{50} (10 mg/L)	No classification available
Marine species				
Crustacean	Acute (96-hours)	Pinoxaden	Data gap	Unknown
Mollusk	Chronic (96-hours)	Pinoxaden	IC_{50} = 0.32 mg a.i./L NOEC = 0.032 mg a.i./L	Highly toxic
Sheepshead minnow	Acute (96-hours)	Pinoxaden	Data gap	Unknown
Marine alga	Acute (96-hours)	Pinoxaden	IC50 = 1.0 mg a.i./L NOEC = 0.62 mg a.i./L	No current classification system

[a] USEPA classification, where applicable

Table 19 Risk to Terrestrial Organisms

Organism	Exposure	Endpoint value	EEC	RQ	Risk
Invertebrates					
Earthworm	Acute Pinoxaden	NOEC = 178 mg/kg	0.027 mg a.i./kg	1.5×10^{-4}	Negligible
	M2	NOEC = 556 mg/kg	0.027 mg/kg	4.9×10^{-5}	Negligible
	M3	NOEC = 178 mg/kg	0.027 mg/kg	1.5×10^{-4}	Negligible
Bee	Oral Pinoxaden AXIAL 100EC ADIGOR (A12127S formulation)	Data gap LD_{50} = 93.0 µg EP/bee NOEL = 9.3 µg EP/bee NOEL = <12.5 µg/bee	0.07 µg a.i./bee 0.55 µg EP/bee 0.58 µg A12127R/bee	0.006 0.06 0.05	Negligible Negligible Negligible
	Contact Pinoxaden AXIAL 100EC ADIGOR (A12127S formulation)	LD_{50} >100 µg a.i./bee NOEC = 6.3 µg a.i./bee LD_{50} = 84.0 µg EP/bee NOEL = 8.4 µg EP/bee NOEL = <12.5 µg/bee	0.07 µg a.i./bee 0.55 µg EP/bee 0.58 µg A12127R/bee	<0.0007 0.01 0.007 0.07 0.05	Negligible Negligible Negligible Negligible Negligible
Birds					
Bobwhite quail	Acute Pinoxaden	LD_{50} >2250 mg a.i./kg bw NOEC 810 mg a.i./kg bw	10.5 mg a.i./kg diet	440 day >1230 day	
	Dietary Pinoxaden	LD_{50} >5970 mg a.i./kg dw NOEC 5970 mg a.i./kg dw	10.5 mg a.i./kg diet	<0.002 0.002	Negligible
	Reproduction M2 (NOA 407854)	NOEC 107 mg/kg dw	10.5 mg a.i./kg diet	0.1	Low
Mallard duck	Dietary Pinoxaden	LD_{50} >5970 mg a.i./kg dw NOEC = 3220 mg a.i./kg dw	2.03 mg a.i./kg diet	<0.002 0.0006	Negligible
	Reproduction M2 (NOA 407854)	NOEC = 1080 mg/kg dw	2.03 mg a.i./kg diet	0.002	Negligible

Organism	Exposure	Endpoint value	EEC	RQ	Risk
Mammals					
Rat	Acute Pinoxaden M3 (NOA 447204) AXIAL 100EC	LD_{50} >5000 mg a.i./kg bw NOEL = 500 mg a.i./kg bw LD_{50} = 1090 mg a.i./kg bw NOEL = 109.8 mg a.i./kg bw LD_{50} = 3129 mg a.i./kg bw NOEL = 312.9 mg a.i./kg bw	30.27 mg a.i./kg diet 30.27 mg a.i./kg diet 311.78 mg/kg diet	>167 day 16.7 day 214 day 21.4 day 59 day 5.9 day	
	Developmental Pinoxaden	NOEL 30 mg a.i./kg bw/day	30.27 mg a.i./kg diet	1.01	Moderate
Mouse	Dietary	NOEL 2500 mg a.i./kg dw	30.09 mg a.i./kg diet	0.012	Negligible
Vascular Plants					
Vascular plant	Seedling emergence AXIAL 100EC ADIGOR (A12127S formulation)	Ryegrass (biomass) EC_{25} = 207.9 g EP/ha EC_{25} = 1480.2 g EP/ha NOEC >4000 g A12127R/ha	618 g EP/ha 618 g EP/ha 645 g A12127R/ha	3.0 0.4 0.2	Moderate Low Low
	Vegetative vigour (AXIAL 100EC)	Pats (biomass) EC_{25} = 53.8 g EP/ha EC_{25} = 990.1 g EP/ha	618 g EP/ha	11.5 0.6	High Low

Table 20 Risk to Aquatic Organisms

Organism	Exposure	Endpoint Value	EEC	RQ	Risk
Freshwater Species					
Daphnia magna	Acute Pinoxaden M2 M3 AXIAL 100EC ADIGOR (A12127S formulation)	Data gap NOEC = 99.0 mg/L NOEC = 56 mg/L Not received NOEC = 0.31 mg/L	0.02 mg a.i./L 0.02 mg/L 0.02 mg/L 0.206 mg/L 0.29 mg/L	Unknown 0.0002 0.0004 Unknown 0.94	Unknown Negligible Negligible Unknown Low to moderate
	Chronic Pinoxaden M2	Data gap NOEC = 5.87 mg/L	0.02 mg/L	Unknown 0.003	Unknown Negligible risk

Organism	Exposure	Endpoint Value	EEC	RQ	Risk
Rainbow trout	Acute				
	Pinoxaden	Data gap	0.02 mg/L	Unknown	Unknown
	M2	NOEC = 105 mg/L	0.02 mg/L	0.0002	Negligible risk
	M3	NOEC = 16 mg/L	0.02 mg/L	0.001	Negligible risk
	AXIAL 100EC	Not received	0.206 mg/L	Unknown	Unknown
	ADIGOR (A12127S formulation)	NOEC = 2.2 mg/L	0.29 mg/L	0.13	Low risk
	Chronic				
	Pinoxaden	Data gap			
Fathead minnow	Acute				
	Pinoxaden	NOEC = 16 mg a.i./L	0.02 mg/L	0.001	Negligible risk
	Chronic				
	Pinoxaden	Data gap	0.02 mg/L	Unknown	Unknown
	M2	Not received		Unknown	Unknown
Freshwater alga	Acute				
Blue-green	Pinoxaden	NOEC = 0.13 mg a.i./L	0.02 mg/L	0.2	Low risk
Green	Pinoxaden	Not received	0.02 mg/L	Unknown	Unknown
	M2	Not received	0.02 mg/L	Unknown	Unknown
	M3	Not received	0.02 mg/L	Unknown	Unknown
	AXIAL 100EC	NOEC = 0.043 mg/L	0.206 mg/L	4.8	Moderate risk
	ADIGOR (A12127S formulation)	NOEC = 0.2 mg/L	0.29 mg/L	1.45	Moderate risk
Diatom	Pinoxaden	Not received	0.02 mg/L	Unknown	Unknown
Vascular plant	Dissolved				
	Pinoxaden	Data gap	0.02 mg/L	Unknown	Unknown
	M2	Not received	0.02 mg/L	Unknown	Unknown
	M3	Not received	0.02 mg/L	Unknown	Unknown
	AXIAL 100EC	Not received	0.206 mg/L	Unknown	Unknown
	ADIGOR (A12127S formulation)	NOEC = 10 mg/L	0.29 mg/L	0.03	Negligible
Marine Species					
Mysid	Acute				
	Pinoxaden	Data gap	0.02 mg a.i./L	Unknown	Unknown
Mollusk	Chronic				
	Pinoxaden	NOEC = 0.032 mg a.i/L	0.02 mg a.i./L	0.6	Low risk
Sheepshead minnow	Acute				
	Pinoxaden	Data gap	0.02 mg a.i./L	Unknown	Unknown
Marine alga	Acute				
	Pinoxaden	NOEC = 0.62 mg a.i./L	0.02 mg/L	0.03	Negligible risk

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